Predictors, symptom dynamics and neural mechanisms of bipolar disorders

Mesbah, R.

Predictors, symptom dynamics and neural mechanisms of bipolar disorders

R. Mesbah

Predictors, symptom dynamics and neural mechanisms of bipolar disorders
Raheleh Mesbah
PhD thesis, Leiden University Medical Center, the Netherlands, 2023

Cover design: Raheleh Mesbah and Benjavisa Ruangvaree Art
Layout: Parham Solaimani
Printed by: Gildeprint

Predictors, symptom dynamics and neural mechanisms of bipolar disorders

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 17 oktober 2023
klokke 13:45 uur

door

Raheleh Mesbah
geboren te Karaj (Iran)
in 1981

Promotors
Prof. dr. A.M. van Hemert

Co-promoters
Dr. E.J. Giltay
Dr. M.A. Koenders

Promotiecommissie
Prof. dr. N.J.A. van der Wee

Prof. dr. B.M. Elzinga
Leiden University

Prof. dr. R.W. Kupka
Amsterdam University Medical Center
University Medical Center Utrecht

Prof. dr. M.H.J. Hillegers
Erasmus University Medical Center

Table of Contents

List of Acronyms

ACC	anterior cingulate cortex
BD	bipolar disorder
BINCO	the Bipolar Netherlands Cohort
dlPFC	dorsolateral prefrontal cortex
DTW	dynamic time warp
EMA	ecological momentary assessment
fMRI	functional magnetic resonance imaging
HC	healthy controls
IFG	inferior frontal gyrus
NESDA	the Netherlands Study of Depression and Anxiety
OFC	orbitofrontal cortex
PFC	prefrontal cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
sgACC	subgenual anterior cingulate cortex
vlPFC	ventrolateral prefrontal cortex
vmPFC	ventromedial prefrontal cortex

CHAPTER 1

General Introduction

Preface

Bipolar disorder (BD) is a chronic and devastating psychiatric disease. It is one of the oldest known psychiatric illnesses, yet many of its features remain elusive. For instance, what are the predictors of the onset and course of the illness? How is it possible to distinguish BD from other psychiatric disorders at an early stage? Are symptoms of the two poles of depression and mania related to each other? And finally, and perhaps most exciting, do patients with BD show different brain activity compared to healthy subjects?

Ancient medical scholars already recognized the syndrome of BD among Greco-Roman, Persian, and Arabic scholars throughout the first millennium CE. Hippocrates (460 - 370 B.C.) was the first physician to recognize BD in ancient Greece. It was described as melancholia (probably what we now recognize as depression) and mania. Later, a Persian physician Avicenna (bu Ali ibn Sina, 980 CE-1037 CE) appeared to have described a type of mixed affective state, a mixture of depression with symptoms of mania such as rapid thoughts, increased sexual drive, extensive anger, and mood lability[1]. He noted that this mixed state with extensive anger is a transitional state from depression to mania—implicitly recognizing the switch phenomenon[2]. In the second millennium CE, Europeans studied BD extensively. The earliest description of a single disorder was in 1684 by Theophilus Bonet (manico-melancholicus). In the late 1800s, Jean-Pierre Falret identified the euthymic state (period free of symptoms) separated from manic and melancholic episodes. In 1902, Emil Kraepelin classified unitary psychosis into two categories. The first category was manic-depression which centered on emotional or mood problems, and the second category was schizophrenia, with thought and cognitive problems as the central features. In the early 1950s, Karl Leonhard differentiated between unipolar depression (major depressive disorder) and bipolar depression and introduced the term bipolar. In 1976, Goodwin and colleagues introduced type II BD as a subtype with episodes of hypomania rather than mania. Finally, in 1980, in the third edition of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM), formal criteria for classification were introduced and BD was established as the current name for the disorder.

Over time, new treatments have helped many patients manage BD and cope with their symptoms. The Australian psychiatrist John Cade discovered lithium as a mood stabilizer for bipolar disorder in 1948. The effectiveness of lithium was demonstrated more thoroughly in the mid-'60s; until now, it is one of the most widely used and studied medications for treating BD. In 1966 valproate was recognized as an effective treatment for acute mania[3]. In 2004 *Olanzapine* was registered as the first atypical antipsychotic for the same indication[4]. Models of BD are predominantly based on biological theories, mainly because evidence from heredity points to a strong genetic basis for this disorder[5]. Consequently, the treatment of BD has been largely based on psychopharmacological intervention. Although there is increasing awareness of the potential importance of psychological interventions in BD, research on psychotherapeutic targets for and effects of BD is still relatively scarce compared to other disorders, such as major depressive disorder.

1.1 Diagnoses of Bipolar disorder and its clinical consequences

BD is a lifelong recurrent mood disorder characterized by alternating or intertwining depressive episodes with elevated mood, which may include mania (BD type I) or hypomania (BD type II). Depression involves low moods, lack of energy or fatigue, lack of interest or pleasure in activities, changes in appetite and sleep pattern, restlessness or irritability, and negative or suicidal thoughts. The manic episode is in many respects the opposite of depression with elevated mood and energy, rapid speech and racing thoughts, less or no need for sleep, grandiose unattainable plans, increased self-esteem, and sometimes psychoses with delusional, hallucinations, and disturbed or illogical thinking. This can lead to impulsive and poor life choices with devastating consequences. When functioning is seriously impaired and if symptoms are present for at least 7 days, we speak of a manic episode. On the contrary, hypomania is an episode of elevated mood in which people generally feel really well for at least four days, but not necessarily with impaired daily functioning. Bipolar disorder type I is defined by experiencing at least one manic episode (with or without a depressive episode), while the diagnosis of bipolar disorder type II includes hypomanic and depressive episodes without a manic episode. In addition to these two types of episodes, the patient can also experience mixed episodes in which depressive and elevated moods can be present at the same time (see Figure 1.1).

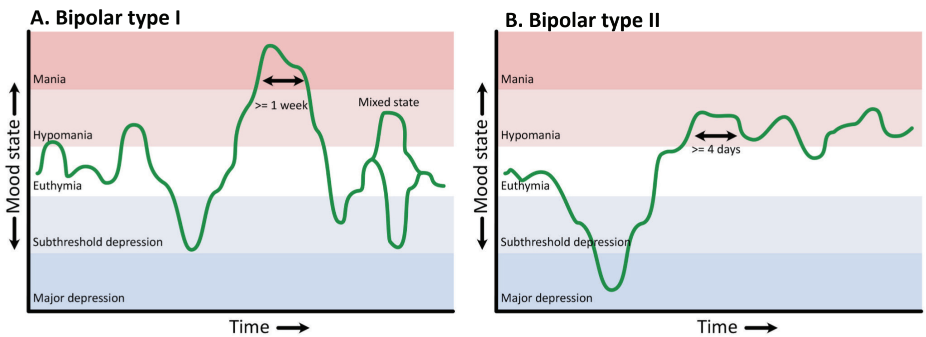


Figure 1.1: Differentiation between bipolar disorder type I (A) and II (B).

The lifetime prevalence estimate of BD I is around 1% and between 1-2 % for BD II[6]. BD is highly heritable, with concordance rates of 65 to 80% in monozygotic twins BD[5, 7]. Regarding gender, men and women are equally affected by BD I, while BD II affects more women[8]. The age of onset of BD is estimated to be between 18-20 years old, with the majority (85%) having an onset with a depressive episode in mid-adolescence (between 15 and 17 years) and the first diagnosable episode of (hypo)mania followed in five years on average[9, 10]. The course of the illness is variable, sometimes with serious functional and cognitive impairment and a reduction in quality of life[11, 12]. Furthermore, about half of BD patients are affected by psychiatric morbidity[13]. Anxiety disorders are the most common comorbid psychiatric condition in patients with BD[14]. Also, substance use is common among comorbid psychiatric conditions, with prevalence rates between 20%

and 70%[15]. The substance used most frequently in people with BD was alcohol (42%), followed by cannabis (20%) and any drug use disorder, mostly cocaine and amphetamines (17%)[16]. Mortality studies have shown that BD is associated with a loss of approximately 10-20 potential years of life[17, 18], and mortality rates are approximately 2-3 times higher than in the general population[19, 20]. The increased mortality is due to medical comorbidity, including diabetes[21] and cardiovascular disease[19, 20], with the latter being the most common cause of premature mortality in BD[22]. Another important reason for increased mortality rates is suicide[23]. In patients with BD, the suicide rate that leads to death is estimated to be 10-30 times higher than that of the general population[23, 24], particularly when BD is not treated[25]. Approximately 20-50% of patients with BD attempt to commit suicide at least once during their lifetime, whereas about 15-20% of attempts are completed[24]. These rates for attempted death and death are about twice those of major depressive disorder[26, 27]. Treatments often result in partial response only, with rates of recurrence of 40%-60% in 1-2 years, even when patients undergo pharmacotherapy[28, 29]. In addition, patients spend up to 47% of their lives in symptomatic states, especially depressive states[30], which emphasizes the need for research to broaden the focus on psychological predictors and neurological research to better understand the complexity of BD.

In the current thesis, we have investigated different domains of BD. First, we examined the predictors of the onset of BD. Second, we investigated the influence of the COVID-19 pandemic as an external stressor that affects the stability of the illness. The interactions of symptoms of BD were then longitudinally examined over time. Finally, the long-term consequences of BD in the field of neurocognitive functioning and brain functioning were investigated.

1.2 Endogenous predictors of the development and course of bipolar disorder

Patients with BD vary considerably in the course, severity, polarity, and cycle pattern of the illness. Apart from the genetic constitution, little is known about the cause of the illness and how certain factors influence its course. Endogenous predictors refer to factors such as genetics or other biological factors, but also psychological factors such as personality factors.

Most patients with BD experience one or more major depressive episodes prior to an initial (hypo)manic episode[31], and as a consequence, will be initially (mis)diagnosed as unipolar depression. However, the treatment of bipolar depression differs from that of patients with BD, where antidepressants are less effective and can even induce (hypo)mania[32]. Therefore, earlier detection of a vulnerability to BD could benefit these patients. Furthermore, risk factors for conversion to BD may provide anchor points for early recognition, psychological interventions, or other appropriate treatment.

Although some neurobiological markers for the development of BD have been identified[33], they are not yet useful for the early recognition of BD in individual patients. Conversion from unipolar depression to BD was predicted by factors that included a parental history of BD, more severe depression, comorbid psychotic symptoms, stressful life events, and childhood trauma[34, 35]. However, these factors are rather generic; a more specific profile might help to better identify the early onset of BD, hopefully with potential for clinical practice. In the current thesis, we examined the predictive value of personality traits and anger in the development of BD.

1.2.1 Personality risk factors

Some personality traits could serve as potential risk factors for the onset of BD. Personality traits are defined in terms of individual differences in self-concept, which are considered stable and consistent and have developed throughout the life of a patient, particularly during childhood[36].

The most common and well-established dimensional measure of personality is the Five-Factor Inventory (NEO-FFI)[37]. The Big Five personality traits are neuroticism, extraversion, openness, agreeableness, and conscientiousness. Evidence from cross-sectional and some prospective studies has shown that higher neuroticism, extraversion, and low agreeableness are more prevalent in BD patients than in healthy controls[38, 39]. It is not clear whether these are also factors that put patients with unipolar depression at risk for BD conversion over time. Examining the predictive value of personality traits might help recognize the early signs of unipolar patients at increased risk for conversion to BD (Chapter 2).

1.2.2 Anger and irritability

Feelings of anger and irritability are prominent symptoms of BD that can occur during (hypo)manic, depressive, and especially mixed mood states. In addition, anger and irritability in unipolar depression appeared to be a robust clinical marker of undiagnosed or subthreshold BD, or so-called bipolar spectrum illness[40]. Evidence from cross-sectional[41, 42] and prospective[43] studies has shown associations between anger and BD. However, the predictive value of anger in conversion to BD has not yet been examined.

Anger may be part of emotion regulation problems, and it has been hypothesized that heightened emotionality is an enduring characteristic of BD[44]. This suggests that people with BD experience more intense and more frequently fluctuating negative and positive emotions (apart from their mood episodes). This might increase their risk of developing mood episodes. Emotional instability in BD can be confused with comorbid personality disorder, since it is a core characteristic of especially cluster B personality disorders (Chapter 3).

1.3 Exogenous predictors of the development and course of bipolar disorder

The exogenous stressor originates from the environment of the individual. This type of decompensation is sometimes called a “reactive" episode. Major stressful life events (e.g., due to loss of a close relative or becoming unemployed) are consistently identified as triggers for mood instability in patients with BD[45]. Stressful live events have also impacted the course of the illness in other ways[35], and have been associated with an increased risk of recurrence and longer recovery time[46, 47].

The ongoing COVID-19 (coronavirus disease 2019) pandemic has had an enormous impact on the lives of people. There has been serious concern about the adverse impact of the pandemic on mental well-being in general, and especially for those with pre-existing mental diseases, including BD[48]. The lockdown measures and restrictions during the pandemic reduced the access of many BD patients to treatment and might have led to social isolation[49]. In addition, the restrictions seemed to interfere, especially with factors such as social rhythm and sleep, which are known triggers for relapse in depression or (hypo)mania[50]. Evidence from cross-sectional studies has shown that the COVID-19 pandemic lockdown was associated with altered biological rhythm (including impaired sleep, activity, and social rhythm) in patients with BD and more frequent depressive episodes[51, 52, 53]. However, to effectively weigh the impact of the COVID-19 outbreak, a comparison of pre-COVID-19 and post-COVID-19 severity levels is needed. Only two studies have investigated the impact of COVID-19 on BD patients using a prospective design. The first study among elderly BD patients (over 50 years) showed no worsening of symptoms of depression or (hypo)mania compared to pre-COVID measurements[54]. The second study showed that BD patients compared to healthy controls were more severely affected by the lockdown restrictions in their biological and social rhythm, income and employment, and pandemic stress. Interestingly, the healthy control group showed an increase in the severity of depressive symptoms during the pandemic compared to the prepandemic scores, while no significant change was observed in patients with BD[55]. More longitudinal studies with pre-COVID-19 measurements are needed to confirm existing findings and examine the effects of the pandemic and strict restrictions on patients with BD (Chapter 4).

1.4 The complex interaction of mania and depressive symptoms

In recent years, there has been a change in the focus of the mental health field from 'group-based models' to more 'personalized models'. The group-based models assume that mental disorders (such as BD) result from an underlying common cause (biological or psychological) leading to a set of symptoms. The common cause approach suggests that most mental diseases, including BD, are in essence homogeneous disorders. The more personalized models suggest that causal patterns may be more heterogeneous and may vary from person to person. One approach to studying individual heterogeneity is the network and complex dynamic system framework. This approach assumes that symptoms themselves might interact and be causally dependent on one another[56, 57]. A simple example of this is that lack of sleep in BD may paradoxically lead to increased energy and/or activity, which in turn leads to more lack of sleep and subsequently to a full-blown manic episode. BD could be approached as a complex dynamic system: *complex* because of the multiple symptom-symptom positive and negative feedback interactions, which might result in disease episodes (either depressive or manic); *dynamic because the* symptom-symptom relations may evolve in an individual over time[58]. In

BD, complex dependencies in time are constantly changing between components (such as mood symptoms and environmental factors), across multiple levels of organization and scale. These components together affect the behavior of the whole, such as manic, euthymic, and depressive mood states, as emergent phenomena[59].

Dynamic time warp (DTW) is a computational algorithm that serves as a network analysis technique to process individual symptom data and takes account of potential non-linear dynamics among symptoms and focuses on change profiles rather than absolute levels of symptom scores[60, 61]. This method is a widely used statistical algorithm, but not yet in the field of psychiatry and psychology. This method helps us investigate the symptom interconnection within panel data when there are only a parse number of time points. It starts with analyzing individual patient data (i.e., idiographic approach, individual level) after which these are aggregated (i.e., nomothetic analysis, group level). This is important as BD is a multicausal, dynamic, and idiosyncratic disorder.

Within a network approach and using DTW, one would be able to study the interactions and relative changes in symptom severity within and between individual patients with BD. This might lead to a better insight into the individual symptom dynamics and help the clinicians in decision-making and personalized treatment (Chapter 5).

1.5 Neurocognitive dysfunctions in BD

In addition to mental and physical health, the neurocognitive function can be affected in patients with BD. Earlier studies have demonstrated that BD is associated with both neurocognitive impairments[62] Several of these deficits are independent of state and can also be present during euthymia[63]. Such characteristics of DB may be considered as trait-, rather than state-related. Neurocognitive deficits include executive functions and working memory[64], which could partly account for functional impairment in patients with BD. Importantly, while 90% of patients attain symptomatic or syndromal recovery, only 30% are fully functional recovered within two years after a severe episode[65]. Cognitive impairment, together with early age of onset and the constant risks of recurrence was shown to lead to the high burden of disease that is seen in patients with BD.

Abnormalities in various brain regions and related circuitry could be underlying cognitive and emotional regulation deficits in BD. Earlier functional MRI studies using cognition- and emotion-related paradigms, have shown alternation in the fronto-limbic network in patients with BD. BD patients appear to show amygdala hyperactivation during emotion processing[66], and increased activity in the orbitofrontal cortex (OFC) during reward processing[67]. Working memory is hypothesized to be related to decreased activity in the PFC[68]. Although there is an increasing number of fMRI studies suggesting fronto-limbic functional abnormalities in BD, a meta-analysis explicitly focussing on this brain network in BD has not yet been performed. A meta-analysis of fronto-limbic network activity in BD is important as malfunctioning regions in this brain network can be considered crucial in the pathophysiology of cognitive and emotional impairments in BD (Chapter 6).

1.6 Aims, research questions, and outline of this dissertation

This dissertation focuses on BD and aims to expand our knowledge of BD by investigating the risk factors for the onset of BD, the effects of COVID-pandamic on the course of BD, the symptom interaction and changes in severity over time, and the functional activity of the brain in BD patients.

It is clear that BD is a complex illness; therefore, it is important to study it from different angles. In this dissertation, we attempted to study both the psychological and neurocognitive aspects of BD. Therefore, the primary purpose of the current dissertation is to study symptoms and identify psychological and fMRI predictors of BD and examine their complex interactions.

The main question of the present dissertation is:

What are predictors for the development and course of BD?

In order to answer these questions, the following sub-questions were formulated:

- *What are endogenous and exogenous predictors for the development and course of BD?*
- *How are symptoms of BD interconnected, and how do they interact over time?*
- *Do BD patients show aberrant brain activity function compared to healthy controls?*

1.6.1 Cohorts used in this dissertation

The current thesis has used data from three different cohorts; the Netherlands Study of Depression and Anxiety (NESDA; Chapters 2 and 3), the Bipolar Netherlands Cohort (BINCO; Chapter 4), and the Bipolar Stress Study (Chapter 5).

NESDA (www.nesda.nl) is an ongoing multi-site naturalistic cohort study that aims to examine the long-term course and consequences of depressive and anxiety disorders[69]. It is a thirteen-year longitudinal cohort study among 2981 participants aged 18 through 65. This cohort included patients with a current or lifetime depressive or anxiety disorder and healthy controls. Participants were recruited from the community (n = 564, 18%), general practice (n = 1,610; 54.0%), and secondary mental healthcare (n = 807; 27.1%). NESDA cohort is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations.

BINCO (www.bincostudie.nl) is an ongoing cohort study in which recently diagnosed (<1 year) bipolar I and II patients are included from different mental health outpatient clinics in the Netherlands. Clinical data such as mood status and received treatment are collected every half year. In addition, cognitive function, lifestyle factors, psychological characteristics, genetic, neuro-imaging, endocrine, and immune status are assessed at baseline and after 1 year. This cohort is funded by Cella Durksz fund.

The Bipolar stress Study is a naturalistic cohort study including 173 BD patients (I and II) who were followed for two years. The first patients were enrolled in 2006, data collection stopped at the end of 2011. The general topic of the Bipolar Stress Study is to identify risk factors that have an impact on the clinical course of BD and the treatment of BD patients. Previously, Spijker et al.[70, 71, 72] and Koenders et al.[35, 73, 74, 75] have reported based on this dataset.

Dissertation outline

In order to answer our main research question (*What are predictors for the development and course of BD?)*, five studies were conducted in the current thesis. Figure 1.2 shows the schematic representation of chapter content for clarification.

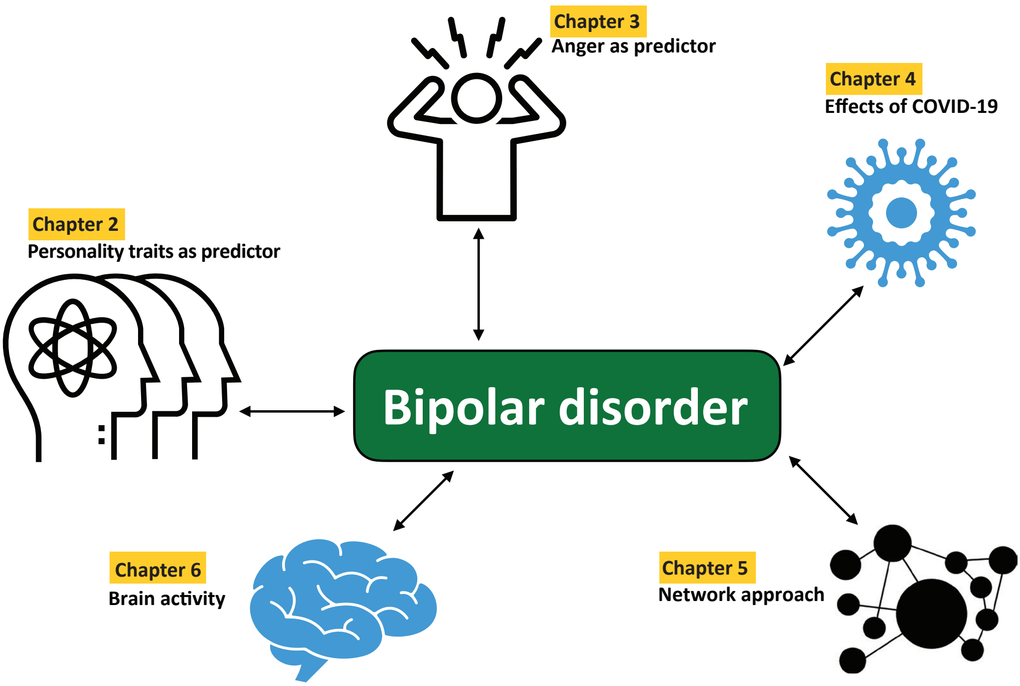


Figure 1.2: Schematic representation of chapter content.

In **Chapter 2**, we aimed to determine which personality traits are independently associated with the development of a (hypo)manic episode within a group of patients who were initially diagnosed with unipolar depression and anxiety disorders. We investigated the influence of personality traits (as baseline predictor) on the incidence of (hypo)manic episodes during the 9-year follow-up. The sub-question was: Can personality traits predict the conversion of BD from unipolar mood disorder during the 9-year follow-up?

In **Chapter 3**, we examined the association of different constructs of anger with BD (cross-sectionally); and second determined the predictive role of aggression reactivity in conversion to BD (prospectively). Can aggression reactivity as a baseline predict the risk of conversion to BD during the 9-year follow-up?

In **Chapter 4,** the effects of COVID-19 on BD were longitudinally investigated in recently diagnosed and relatively young adults with BD (diagnosis $<$ 1 year), who were followed from the first months of the Dutch lockdown restrictions into the period in which measures were temporarily eased. In this study, we compared mania, depression, anxiety, and stress-related symptom levels before the pandemic with levels during the pandemic using up to six follow-up measurements. We hypothesized that patients with newly onset BD were at increased risk of both mania and depression due to increased stress and quarantine measures of the COVID-19 pandemic.

In **Chapter 5**, we investigated interactions and relative changes in symptom severity within and between BD patients. We used a novel technique of DTW (network approach) to analyze the dynamics of symptoms over time and utilized symptoms of BD repeatedly (every 3 to 6 months) to assess depression and manic symptoms in 141 patients with BD. The sub-question was: how are symptoms of BD interconnected, and how do they interact over time in patients with BD (within and between patients)?

In **Chapter 6**, we performed an fMRI meta-analysis to investigate the brain functioning of BD patients compared with healthy controls (HC) in three domains: emotion processing, reward processing, and working memory. The sub-question was: do BD patients show aberrant brain activity function compared to healthy controls?

Finally, in **Chapter 7**, we summarized and discussed the findings alongside a number of implications for research and practice.

Bibliography

1. Ghaemi SN, Nassir Ghaemi S, and Mauer S. *Diagnosis, classification, and differential diagnosis of mood disorders*. 2020.
2. Haque A. “Psychology from Islamic Perspective: Contributions of Early Muslim Scholars and Challenges to Contemporary Muslim Psychologists”. In: *J. Relig. Health* 43.4 (2004), pp. 357–377.
3. Jochim J, Rifkin-Zybutz RP, Geddes J, and Cipriani A. “Valproate for acute mania”. In: *Cochrane Database Syst. Rev.* 10 (2019), p. CD004052.
4. Tohen M et al. “Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial”. In: *Am. J. Psychiatry* 162.7 (2005), pp. 1281–1290.
5. Fabbri C. “The Role of Genetics in Bipolar Disorder”. In: *Curr. Top. Behav. Neurosci.* 48 (2021), pp. 41–60.
6. Merikangas KR et al. “Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative”. In: *Arch. Gen. Psychiatry* 68.3 (2011), pp. 241–251.
7. Johansson V, Kuja-Halkola R, Cannon TD, Hultman CM, and Hedman AM. “A population-based heritability estimate of bipolar disorder - In a Swedish twin sample”. In: *Psychiatry Res.* 278 (2019), pp. 180–187.
8. Nivoli AMA et al. “Gender differences in a cohort study of 604 bipolar patients: the role of predominant polarity”. In: *J. Affect. Disord.* 133.3 (2011), pp. 443–449.
9. Duffy A, Goodday S, Keown-Stoneman C, and Grof P. “The Emergent Course of Bipolar Disorder: Observations Over Two Decades From the Canadian High-Risk Offspring Cohort”. In: *Am. J. Psychiatry* 176.9 (2019), pp. 720–729.
10. Mesman E, Nolen WA, Reichart CG, Wals M, and Hillegers MHJ. “The Dutch bipolar offspring study: 12-year follow-up”. In: *Am. J. Psychiatry* 170.5 (2013), pp. 542–549.
11. Martinez-Aran A et al. “Functional outcome in bipolar disorder: the role of clinical and cognitive factors”. In: *Bipolar Disord.* 9.1-2 (2007), pp. 103–113.

12. Grande I et al. “Occupational disability in bipolar disorder: analysis of predictors of being on severe disablement benefit (PREBIS study data)”. In: *Acta Psychiatr. Scand.* 127.5 (2013), pp. 403–411.
13. McIntyre RS, Konarski JZ, and Yatham LN. “Comorbidity in bipolar disorder: a framework for rational treatment selection”. In: *Hum. Psychopharmacol.* 19.6 (2004), pp. 369–386.
14. Yapici Eser H, Kacar AS, Kilciksiz CM, Yalçinay-Inan M, and Ongur D. “Prevalence and Associated Features of Anxiety Disorder Comorbidity in Bipolar Disorder: A Meta-Analysis and Meta-Regression Study”. In: *Front. Psychiatry* 9 (2018), p. 229.
15. McElroy SL et al. “Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder”. In: *Am. J. Psychiatry* 158.3 (2001), pp. 420–426.
16. Hunt GE, Malhi GS, Cleary M, Lai HMX, and Sitharthan T. “Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990–2015: Systematic review and meta-analysis”. In: *J. Affect. Disord.* 206 (2016), pp. 331–349.
17. Laursen TM. “Life expectancy among persons with schizophrenia or bipolar affective disorder”. In: *Schizophr. Res.* 131.1-3 (2011), pp. 101–104.
18. Kessing LV, Vradi E, and Andersen PK. “Life expectancy in bipolar disorder”. In: *Bipolar Disord.* (2015).
19. Crump C, Sundquist K, Winkleby MA, and Sundquist J. “Comorbidities and mortality in bipolar disorder: a Swedish national cohort study”. In: *JAMA Psychiatry* 70.9 (2013), pp. 931–939.
20. Laursen TM et al. “Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries”. In: *PLoS One* 8.6 (2013), e67133.
21. Calkin CV, Gardner DM, Ransom T, and Alda M. “The relationship between bipolar disorder and type 2 diabetes: more than just co-morbid disorders”. In: *Ann. Med.* 45.2 (2013), pp. 171–181.
22. Kessing LV, Vradi E, McIntyre RS, et al. “Causes of decreased life expectancy over the life span in bipolar disorder”. In: *J. Affect. Disord.* (2015).
23. Dome P, Rihmer Z, and Gonda X. “Suicide Risk in Bipolar Disorder: A Brief Review”. In: *Medicina* 55.8 (2019).
24. Schaffer A et al. “International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder”. In: *Bipolar Disord.* 17.1 (2015), pp. 1–16.
25. Gibbons RD, Hur K, Brown CH, et al. “Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder”. In: *Arch. Gen. Psychiatry* (2009).
26. Owens D, Horrocks J, and House A. “Fatal and non-fatal repetition of self-harm. Systematic review”. In: *Br. J. Psychiatry* 181 (2002), pp. 193–199.
27. Turecki G et al. “Suicide and suicide risk”. In: *Nat Rev Dis Primers* 5.1 (2019), p. 74.

28. Angst J, Gamma A, Sellaro R, Lavori PW, and Zhang H. "Recurrence of bipolar disorders and major depression. A life-long perspective". In: *Eur. Arch. Psychiatry Clin. Neurosci.* 253.5 (2003), pp. 236–240.
29. Gitlin MJ, Swendsen J, Heller TL, and Hammen C. "Relapse and impairment in bipolar disorder". In: *Am. J. Psychiatry* 152.11 (1995), pp. 1635–1640.
30. Judd LL et al. "The long-term natural history of the weekly symptomatic status of bipolar I disorder". In: *Arch. Gen. Psychiatry* 59.6 (2002), pp. 530–537.
31. Perlis RH et al. *Revisiting Depressive-Prone Bipolar Disorder: Polarity of Initial Mood Episode and Disease Course Among Bipolar I Systematic Treatment Enhancement Program for Bipolar Disorder Participants.* 2005.
32. Bowden CL. "A different depression: clinical distinctions between bipolar and unipolar depression". In: *J. Affect. Disord.* 84.2-3 (2005), pp. 117–125.
33. Vai B, Bertocchi C, and Benedetti F. *Cortico-limbic connectivity as a possible biomarker for bipolar disorder: where are we now?* 2019.
34. Musliner KL and Østergaard SD. "Patterns and predictors of conversion to bipolar disorder in 91 587 individuals diagnosed with unipolar depression". In: *Acta Psychiatr. Scand.* 137.5 (2018), pp. 422–432.
35. Koenders MA et al. "Stressful life events in bipolar I and II disorder: cause or consequence of mood symptoms?" In: *J. Affect. Disord.* 161 (2014), pp. 55–64.
36. Zaninotto L et al. "A meta-analysis of temperament and character dimensions in patients with mood disorders: Comparison to healthy controls and unaffected siblings". In: *J. Affect. Disord.* 194 (2016), pp. 84–97.
37. Costa Jr PT and McCrae RR. "Domains and facets: hierarchical personality assessment using the revised NEO personality inventory". In: *J. Pers. Assess.* 64.1 (1995), pp. 21–50.
38. Bukh JD, Andersen PK, and Kessing LV. "Personality and the Long-Term Outcome of First-Episode Depression: A Prospective 5-Year Follow-Up Study". In: *J. Clin. Psychiatry* 77.6 (2016), e704–10.
39. Sparding T, Pålsson E, Joas E, Hansen S, and Landén M. "Personality traits in bipolar disorder and influence on outcome". In: *BMC Psychiatry* 17.1 (2017), p. 159.
40. Benazzi F and Akiskal H. "Irritable-hostile depression: further validation as a bipolar depressive mixed state". In: *J. Affect. Disord.* 84.2-3 (2005), pp. 197–207.
41. Benazzi F and Akiskal HS. "Psychometric delineation of the most discriminant symptoms of depressive mixed states". In: *Psychiatry Res.* 141.1 (2006), pp. 81–88.
42. Perlis RH, Brown E, Baker RW, and Nierenberg AA. "Clinical features of bipolar depression versus major depressive disorder in large multicenter trials". In: *Am. J. Psychiatry* 163.2 (2006), pp. 225–231.
43. Ballester J et al. "Prospective longitudinal course of aggression among adults with bipolar disorder". In: *Bipolar Disord.* 16.3 (2014), pp. 262–269.
44. Henry C et al. "Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period". In: *Psychiatry Res.* 159.1-2 (2008), pp. 1–6.
45. Lex C, Bäzner E, and Meyer TD. "Does stress play a significant role in bipolar disorder? A meta-analysis". In: *J. Affect. Disord.* 208 (2017), pp. 298–308.

46. Hammen C and Gitlin M. “Stress reactivity in bipolar patients and its relation to prior history of disorder”. In: *Am. J. Psychiatry* 154.6 (1997), pp. 856–857.

47. Johnson SL and Miller I. “Negative life events and time to recovery from episodes of bipolar disorder”. In: *J. Abnorm. Psychol.* 106.3 (1997), pp. 449–457.

48. Stefana A et al. “The COVID-19 pandemic is a crisis and opportunity for bipolar disorder”. In: *Bipolar Disord.* 22.6 (2020), pp. 641–643.

49. Dalkner N et al. “Psychological and behavioral response on the COVID-19 pandemic in individuals with bipolar disorder: A multicenter study”. In: *Psychiatry Res.* 310 (2022), p. 114451.

50. Takaesu Y. “Circadian rhythm in bipolar disorder: A review of the literature”. In: *Psychiatry Clin. Neurosci.* 72.9 (2018), pp. 673–682.

51. Carta MG et al. “Living With Bipolar Disorder in the Time of Covid-19: Biorhythms During the Severe Lockdown in Cagliari, Italy, and the Moderate Lockdown in Tunis, Tunisia”. In: *Front. Psychiatry* 12 (2021), p. 634765.

52. Karantonis JA, Rossell SL, Berk M, and Van Rheenen TE. “The mental health and lifestyle impacts of COVID-19 on bipolar disorder”. In: *J. Affect. Disord.* 282 (2021), pp. 442–447.

53. Van Rheenen TE et al. “Mental health status of individuals with a mood-disorder during the COVID-19 pandemic in Australia: Initial results from the COLLATE project”. In: *J. Affect. Disord.* 275 (2020), pp. 69–77.

54. Orhan M et al. “Psychiatric symptoms during the COVID-19 outbreak in older adults with bipolar disorder”. In: *Int. J. Geriatr. Psychiatry* 36.6 (2021), pp. 892–900.

55. Yocum AK, Zhai Y, McInnis MG, and Han P. “Covid-19 pandemic and lockdown impacts: A description in a longitudinal study of bipolar disorder”. In: *J. Affect. Disord.* 282 (2021), pp. 1226–1233.

56. Fried EI and Nesse RM. “Depression sum-scores don’t add up: why analyzing specific depression symptoms is essential”. In: *BMC Med.* 13 (2015), p. 72.

57. Borsboom D et al. “Network analysis of multivariate data in psychological science”. In: *Nature Reviews Methods Primers* 1.1 (2021), pp. 1–18.

58. Cramer AOJ et al. “Major Depression as a Complex Dynamic System”. In: *PLoS One* 11.12 (2016), e0167490.

59. Fried EI and Cramer AOJ. “Moving Forward: Challenges and Directions for Psychopathological Network Theory and Methodology”. In: *Perspect. Psychol. Sci.* 12.6 (2017), pp. 999–1020.

60. Zhang L et al. “Distinct temporal brain dynamics in bipolar disorder and schizophrenia during emotion regulation”. In: *Psychol. Med.* 50.3 (2020), pp. 413–421.

61. Farruggia MC, Laird AR, and Mattfeld AT. “Common default mode network dysfunction across psychopathologies: a neuroimaging meta-analysis of the n-back working memory paradigm”. In: *bioRxiv* (2020), pp. 2020–.

62. Martinez-Aran A et al. “Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder”. In: *Am. J. Psychiatry* 161.2 (2004), pp. 262–270.

63. Martinez-Aran A and Vieta E. “Cognition as a target in schizophrenia, bipolar disorder and depression”. In: *Eur. Neuropsychopharmacol.* 25.2 (2015), pp. 151–157.
64. Bourne C et al. “Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis”. In: *Acta Psychiatr. Scand.* 128.3 (2013), pp. 149–162.
65. Tohen M et al. “Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features”. In: *Am. J. Psychiatry* 157.2 (2000), pp. 220–228.
66. Phillips ML, Travis MJ, Fagiolini A, and Kupfer DJ. “Medication effects in neuroimaging studies of bipolar disorder”. In: *Am. J. Psychiatry* 165.3 (2008), pp. 313–320.
67. Norwood MF et al. “Brain activity, underlying mood and the environment: A systematic review”. In: *J. Environ. Psychol.* 65 (2019), p. 101321.
68. McKenna BS, Sutherland AN, Legenkaya AP, and Eyler LT. *Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder.* 2014.
69. Penninx BWJH et al. “The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods”. In: *Int. J. Methods Psychiatr. Res.* 17.3 (2008), pp. 121–140.
70. Spijker AT et al. “Functional polymorphism of the glucocorticoid receptor gene associates with mania and hypomania in bipolar disorder”. In: *Bipolar Disord.* 11.1 (2009), pp. 95–101.
71. Spijker AT et al. *Glucocorticoid and mineralocorticoid receptor polymorphisms and clinical characteristics in bipolar disorder patients.* 2011.
72. Manenschijn L et al. *Long-term cortisol in bipolar disorder: Associations with age of onset and psychiatric co-morbidity.* 2012.
73. Koenders MA et al. “The bidirectional impact of perceived and enacted support on mood in bipolar outpatients: A two-year prospective study”. In: *Compr. Psychiatry* 60 (2015), pp. 59–67.
74. Koenders MA et al. “Effects of mood state on divided attention in patients with bipolar disorder: evidence for beneficial effects of subclinical manic symptoms”. In: *Psychiatry Res.* 220.1-2 (2014), pp. 302–308.
75. Koenders MA et al. “A Network Approach to Bipolar Symptomatology in Patients with Different Course Types”. In: *PLoS One* 10.10 (2015), e0141420.

CHAPTER 2

Personality traits and the risk of incident (Hypo)mania among subjects initially suffering from depressive and anxiety disorders in a 9-year cohort study

Mesbah, R., Koenders, M. A., Spijker, A. T., de Leeuw, M., Boschloo, L., Penninx, B. W. J. H., van Hemert, A. M., & Giltay, E. J. (2019). Personality traits and the risk of incident (hypo)mania among subjects initially suffering from depressive and anxiety disorders in a 9-year cohort study. *Journal of Affective Disorders*, 259, 451-457.
DOI: 10.1016/j.jad.2019.08.043

Abstract

Background
Bipolar disorder (BD) is characterized by the alternating occurrence of (hypo)manic and depressive episodes. The aim of the current study was to determine whether personality traits independently predicted the subsequent development of (hypo)manic episodes within a group of patients who were initially diagnosed with depressive and anxiety disorders.

Methods
The Netherlands Study of Depression and Anxiety is a cohort study with measurements taken at baseline and at 2-, 4-, 6-, and 9-year follow-up. Development of a (hypo)manic episode during follow-up was assessed with the Composite International Diagnostic Interview and (hypo)manic symptoms were evaluated with the Mood Disorder Questionnaire. The Big Five personality traits were the independent variables in multivariable Cox regression analyses.

Results
There were 31 incident cases of (hypo)manic episodes (n = 1,888, mean age 42.5 years, 68.3% women), and 233 incident cases of (hypo)manic symptoms (n = 1,319, mean age 43.1, 71.9% women). In multivariable analyses, low agreeableness was independently associated with an increased risk of developing a (hypo)manic episode, with a hazard ratio (HR) of 0.54 ($p = 0.002$, 95% CI [0.37, 0.78]). This finding was consistent with the development of (hypo)manic symptoms (HR 0.77, $p = 0.001$, 95% CI [0.66, 0.89]).

Limitations
The 2-year lag-time analysis reduced the number of participants at risk of a (hypo)manic episode.

Conclusions
We conclude that low agreeableness is a personality-related risk factor for incident (hypo)mania among subjects initially suffering from depressive and anxiety disorders. Increased attention to personality deviances could help to recognize BD at an early stage.

2.1 Introduction

Bipolar disorder (BD) is a common mood disorder characterized by alternating periods of (hypo)mania and depression. The lifetime prevalence of BD is estimated around 1% for bipolar I disorder (BDI) and between 1 and 2% for bipolar II disorder (BDII)[1, 2, 3].

A majority of patients with BD experience one or more major depressive episodes prior to an initial (hypo)manic episode[1, 4]. Being able to identify unipolar depressed patients who are at high risk for developing a (hypo)manic episode would help to develop early intervention strategies that could be tailored to target BD. Although increasing numbers of neurobiological markers for the development of BD have been identified[5], these are not yet useful for the early recognition of BD in individual patients in daily clinical practice. More easily assessable psychological variables may be more suitable. Conversion from unipolar depression to BD was predicted by factors including a parental history of BD, more severe depression, comorbid psychotic symptoms, and childhood trauma[4, 6, 7]. However, these factors are rather generic; a more specific profile might help to further identify the early onset of BD. In this study, we focus specifically on personality traits as a risk factor. We investigated whether personality traits independently predicted incidence of (hypo)mania in a group of patients with depressive or anxiety disorder.

Personality traits might also help to identify a "bipolar profile". Personality traits are defined in terms of individual differences in self-concept, which is considered stable and consistent and has developed across a patient's lifespan—particularly during childhood[8]. Previous studies that attempted to identify the personality profile of BD have used different approaches, such as hyperthymic, cyclothymic, and dysthymic temperaments[9]; the hypomanic personality traits[10]; the behavioral inhibition/approach system (BIS/BAS)[11]; and the Big Five personality traits. In the current study, we used the more common Big Five personality traits approach. The Big Five personality traits are neuroticism, extraversion, openness, agreeableness, and conscientiousness, and these are often assessed using the Neuroticism, Extraversion, Openness Five-Factor Inventory (NEO-FFI) questionnaire[12]. However, unlike research on unipolar depressive disorder, only a limited number of studies have focused on the putative association between BD and personality traits[13, 14, 15].

There have been some cross-sectional studies on the Big Five personality traits and BD. Several studies have shown that BD patients have higher neuroticism compared with unipolar depression patients and healthy controls[16, 17, 18, 19, 20]. Higher extraversion in BD patients compared with unipolar depression patients and controls was found in the majority of studies[18, 21, 22, 23, 24]. Patients with BD also demonstrated higher openness compared with healthy controls and other psychiatric groups[24]. In addition, low agreeableness was associated with BD in two cross-sectional studies[16, 20].

Previous prospective findings have been categorized according to the "conversion literature"—i.e., focusing on patient samples with current depressive disorders[15] —or according to the "prediction literature"—i.e., including bipolar patients and/or participants without a current disorder (e.g., healthy participants from the general population)[14, 25].

The "prediction literature" has shown high extraversion and low agreeableness to be independent risk factors for the development of a (hypo)manic episode in bipolar patients[14, 15, 25, 26]. Three previous prediction studies have included 39[14, 15, 25, 26], 110[14], and 2,247[25] patients with BD and/or healthy participants. These studies had follow-up durations ranging from 6 months[14, 15, 25, 26] to 2 years[14, 25]. These studies consistently showed high neuroticism, high extraversion, and low agreeableness as predictors of manic symptoms[14, 25], but showed different results for high conscientiousness[26].

Only one “conversion" study examined the predictive value of personality traits and conversion to BD[15] with 5 years of follow-up. These findings showed that higher extraversion scores predicted conversion to BD among patients with major depression ($N = 301$), even after adjusting for symptom severity. In the same study, neuroticism was not a predictor for conversion to BD.

In sum, there is evidence from cross-sectional and some prospective studies that higher neuroticism and extraversion and low agreeableness are more prevalent in BD patients than healthy controls. Whether these are also factors that put patients with other affective disorders at risk for developing BD over time is not clear. Larger cohort studies with longer follow-up periods are needed to determine whether and to what extent such traits independently predict the risk of a (hypo)manic episode.

The aim of the current study was to determine whether personality traits independently predicted the subsequent development of (hypo)manic episodes within a group of patients who were initially diagnosed with depressive and anxiety disorders. This was a well-characterized, large, prospective cohort study with a 9-year follow-up period. Since the comorbidity between depression and anxiety is high, and patients with anxiety are at increased risk of BD[27], we also included patients with anxiety disorders. We used survival analysis to investigate the influence of personality traits on incidence of (hypo)manic symptoms and episodes during the 9-year follow-up. Based on previous findings[14, 15, 25, 26], we hypothesized that traits such as higher extraversion and lower agreeableness would have independent predictive value regarding the onset of (hypo)manic symptoms or a (hypo)manic episode.

2.2 Methods

2.2.1 Subjects

Data were obtained from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is a prospective cohort study with measurement points at baseline and at the 2-, 4-, 6-, and 9-year follow-up. At baseline, 2,981 participants were included—of whom 2,483 (83.3%) participated in at least one of the follow-ups. We included only those participants with current and remitted depressive and/or anxiety disorder ($n = 1,888$; 63.3%) in our analyses. The total percentage of participants (of 2,981) who participated at each follow-up were 87.1% (2 year), 80.6% (4 year), 75.7% (6 year), and 69.4% (9 year). As we selected only those participants with data available from at least two follow-ups, the number of included participants in our sample were: 1,888 (100.0%) at 2 years, 1,673 (88.6%) at 4 years, 1,563 (82.8%) at 6 years, and 1,434 (76.0%) at 9 years. These participants were between 18 and 65 years of age at baseline and suffered from remitted

(n = 560) or current (n = 1,328) depressive and/or anxiety disorders. Recruitment took place in primary health care and outpatient mental care facilities as well as in communities from the area around Amsterdam, Leiden, and Groningen (the Netherlands). We used the following criteria for exclusion: (a) a primary clinical diagnosis of BD, psychotic disorder, obsessive-compulsive disorder, or severe addiction disorder, and (b) insufficient Dutch language skills. The study design has been extensively described previously[28]. The research protocol was approved by the Ethical Committee of participating universities and all participants provided written informed consent.

For the current study, we selected patients suffering from remitted or current depressive and/or anxiety disorders who had completed at least one follow-up assessment. One hundred and seventeen (6.2%) participants missed one of the CIDI measurements, but participated in the follow-ups. Only one of these 117 participants eventually developed a (hypo)manic episode. Remitted or current depressive and/or anxiety disorders were assessed using the Composite International Diagnostic Interview (CIDI, version 2.1), and specially trained research staff administered the diagnostic interviews.

2.2.2 Measures

Outcome variables. At the 9-year follow-up, a number of individuals experienced a (hypo)manic episode or symptoms thereof. The BD section of the CIDI was not conducted at baseline; therefore, it was not possible to exclude BD patients with certainty at baseline. However, the NESDA had already excluded patients with a self-reported or with a professionally reported primary clinical diagnosis of BD during the initial participant screening. A lag-time analysis of 2 years was applied, meaning that all incidents of (hypo)manic cases based on the CIDI between baseline and the 2-year follow-up were excluded.

CIDI (hypo)manic episodes. The incident cases of (hypo)manic episodes, which were indicative of BD, were ascertained using the CIDI. Trained researchers administered the BD section of the CIDI. The onset of a (hypo)manic episode was based on the presence of a DSM-IV hypomanic or manic episode as assessed with the BD section of the CIDI at the 2-, 4-, 6-, and 9-year follow-up assessments. In the analyses of (hypo)manic episodes, we excluded all participants who met the criteria based on the CIDI between baseline and the 2-year follow-up (n = 86; 71.7% within percentage). Thus, incidents of (hypo)mania were analyzed in 1,888 participants; of these participants, 31 (1.6%) experienced an incidence of (hypo)mania.

The CIDI is highly reliable (BDI: $\kappa = 0.92$, BDII: $\kappa = 0.94$)[29] and is a valid instrument (diagnosis of a lifetime BD sensitivity 0.87 and specificity 0.89)[30] for yielding diagnoses listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

Mood Disorder Questionnaire (MDQ) of (hypo)manic symptoms. The MDQ is a screening instrument for a history of (hypo)manic symptoms, which for the sake of brevity, we will refer to as “(hypo)manic symptoms". The history of (hypo)manic symptoms was ascertained in all participants during and up to the 9-year follow-up using the MDQ[31].

The MDQ was conducted at baseline and at 2-, 4-, 6-, and 9-year follow-up. The MDQ includes 15 items and consists of three parts. The first part comprises 13 dichotomous items regarding BD symptoms. The second part assesses the clustering of symptoms, and the third part relates to disease severity. To define (hypo)manic symptoms based on the MDQ, we used the cut-off that was defined in prior NESDA research[32], with slightly modified criteria compared with the most commonly used cut-off according to Hirschfeld[33]. We considered the MDQ total score to show (hypo)manic symptoms when at least seven positive answers were given from a total of 13 items—irrespective of answers on the second or third part. This cut-off demonstrated good psychometric properties when detecting (hypo)manic symptoms, with a sensitivity of 0.83 and a specificity of 0.82[32]. In addition, we excluded all patients who met the criteria for (hypo)manic symptoms based on the MDQ baseline cut-off (n = 450; 80.4% with percentage), which we used to analyze our data for (hypo)manic symptoms. In the end, we analyzed the incidents of (hypo)manic symptoms in a total of 1,319 participants, of whom 233 (17.7%) experienced (hypo)manic symptoms.

2.2.3 Baseline Predictor

Personality traits. Personality traits were determined using the NEO-FFI at baseline, which is a short version of NEO Personality Inventory (NEO-PI-R)[12]. The widely used NEO-FFI is a 60-item self-report questionnaire that measures items on a five-point scale (ranging from 0 to 4). This questionnaire measures personality traits within five main personality domains (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) each listing 12 items. For each broad domain, item clusters of subcomponents are grouped together, and these mirror the facets of the NEO-PI-R[34].

Internal consistencies for the current study were calculated for the participants NEO-FII domains and yielded Cronbach's α =.90 for neuroticism, Cronbach's α =.78 for extraversion, Cronbach's α =.63 for openness, Cronbach's α =.70 for agreeableness, and Cronbach's α =.79 for conscientiousness. In short, neuroticism includes emotional instability and negative effects. Extraversion is seen as being sociable, assertive, and excited Openness includes intellectual curiosity, need for variety, and non-dogmatic attitudes. Agreeableness involves trust, altruism, and sympathy; individuals who score low on agreeableness tend to be less cooperative and more competitive. Conscientiousness is the predisposition to being disciplined and striving after goals, and a strict adherence to principles[12].

Symptom severity. The current presence of anxiety and/or depressive disorders in patients was assessed according to the respective sections of the DSM-IV, based on the CIDI interview (WHO version 2.1), which has high interrater reliability (any depressive disorder $\kappa = 0.95$)[29] and high validity for depressive and anxiety disorders[35].

The severity of depression was found to be a potential risk factor for the development of a (hypo)manic episode[36]; therefore, we included this as a covariate in the current study. We assessed the severity of depression based on the 30-item self-report Inventory of Depressive Symptomatology (IDS)[37], which has an internal consistency of Cronbach's α =.94. The baseline total score was used as a covariate in the analysis.

Because many patients suffered from anxiety, we adjusted for the severity of anxiety symptoms, which we assessed according to the Beck Anxiety Inventory (BAI). This is a 21-item self-report inventory with an internal consistency of Cronbach's α =.92[38].

Childhood trauma also predicted the onset of a (hypo)manic episode) and was included as a covariate. Childhood trauma was assessed with the Childhood Trauma Inventory, which is a cumulative index ranging from 0 to 8 that considers the frequency of emotional neglect, psychological abuse, physical abuse, and sexual abuse before the age of 16 years[39].

2.3 Statistical Analysis

We used analyses of variance and χ^2 tests to conduct basic descriptive statistics. The presence of a (hypo)manic episode according to the CIDI was determined at the 4-, 6-, and 9-year follow-up because we applied a lag-time of 2 years. The presence of (hypo)manic symptoms according to the MDQ was determined at each of the time points. We used Cox proportional hazard models to examine the relationship between baseline personality traits and incidence of (hypo)manic episodes and symptoms separately. The date of inclusion into the cohort was considered the baseline for each patient in the survival analysis. The primary endpoint consisted of all incident cases during the follow-up period, the survival time (including all incident cases of [hypo]manic episodes or symptoms), and the diagnoses at each time point (based on either the CIDI or the MDQ). We censored all follow-up losses as well as patients who did not experience a (hypo)manic episode or symptoms thereof during follow-up. We checked the proportional-hazards assumptions with log-minus-log plots using personality-domain scores categorized into tertiles. These curves did not show any violation, except for a slight violation of the openness personality domain. All personality (sub)domain scores were standardized into z scores. We estimated three models: (a) a crude model that did not include covariates, (b) an adjusted model that included sociodemographic data (i.e., age, gender, and education in years), and current depressive/anxiety disorder based on the CIDI, and (c) a fully adjusted model that included the remaining four Big Five personality traits, severity of depression and anxiety symptoms, childhood trauma, and alcohol dependence. Finally, we used Pearson's correlation to examine the relationship between the Big Five personality traits and the severity of depression and neuroticism.

Two-sided p values were considered statistically significant at the 0.05 level. All analyses were conducted using IBM SPSS statistics software, version 22 (IBM Corp., Armonk, NY, USA).

2.4 Results

2.4.1 Baseline Characteristics

Table 2.1 includes a summary of the basic demographic and clinical characteristics of (hypo)manic episodes and symptoms of all participants. There were 31 cases of (hypo)manic episodes (n = 1,888, mean age = 42.5 years, 68.3% women), and 233 cases of (hypo)manic symptoms (MDQ total score >7) (n = 1,319, mean age = 43.1 years, 71.9% women). The included subjects (based on analyses of [hypo]manic episodes) were on average 42.5 years of age (SD = 12.6) and were predominantly female (68.3%). They also had an average 12.1 years (SD = 3.3) of education.

At baseline, the mean IDS-SR was 24.3 (SD = 13.1), and the mean BAI was 13.5 (SD = 10.2), indicating overall mild depressive and anxiety symptoms. Next, the results of Pearson's correlation between the Big Five personality traits and the severity of depression showed strong associations of neuroticism with IDS-SR (r =.69, p <.001). The other Big Five personality traits were negatively correlated with IDS-SR: extraversion (r = - 0.49, p <.001), openness (r = -.11, p <.001), agreeableness (r = -.28, p <.001), and conscientiousness (r = -.34, p <.001). Moreover, there were only three incident cases of (hypo)manic episodes in patients with remitted depressive and/or anxiety disorders and 28 incident cases of (hypo)manic episodes in patients with current depressive and/or anxiety disorders. When looking to the overlap between the CIDI and MDQ, four (12.9%, N = 31) participants met the criteria of a (hypo)manic episode based on the CIDI but did not have a positive MDQ score.

2.4.2 Predictors of Incident (Hypo)manic Episodes

In the crude models, all the personality domains were significantly associated with subsequent (hypo)manic episodes except for the openness and extraversion domains. In the adjusted models, high neuroticism and low agreeableness remained significant risk factors for the development of a (hypo)manic episode. The hazard ratios (HRs) were 1.70 ($p <$ 0.04, 95% CI [1.03, 2.82]) for neuroticism and 0.52 ($p <$ 0.001, 95% CI [0.37, 0.74]) for agreeableness. In the fully adjusted model, however, only low agreeableness remained an independently associated risk factor for incidence of (hypo)manic episodes (HR 0.54, p = 0.002, 95% CI [0.37, 0.78]) (see Table 2.1).

Kaplan-Meier curves categorized into tertiles show that lower levels of agreeableness were associated with a higher incidence of (hypo)manic episodes (see Figure 2.1A). This finding is in accordance with those from Cox regression models.

	Analyses of (hypo)manic episodes (n = 1,888)	**Analyses of (hypo)manic symptoms** (n = 1,319)
Sociodemographics		
Female sex, no. (%)	1,290 (68.3)	948 (71.9)
Age in years, mean (*SD*)	42.5 (12.6)	43.1 (12.6)
Education in years, mean (*SD*)	12.1 (3.3)	12.3 (3.3)
BMI, kg/m^2, mean (*SD*)	25.7 (5.1)	25.7 (5.0)
Smoking, no. (%)	737 (39.0)	447 (33.9)
Alcohol dependency/abuse, no. (%)	549 (29.1)	312 (23.7)
Clinical characteristics		
Severity measures		
IDS-SR total score, mean (*SD*)	24.3 (13.1)	22.4 (13.0)
BAI total score, mean (*SD*)	13.5 (10.2)	12.5 (9.8)
Medication use		
Benzodiazepines, no. (%)	335 (17.7)	230 (17.4)
SSRI, no. (%)	411 (21.8)	291 (22.1)
TCA, no. (%)	63 (3.3)	49 (3.7)
Other AD, no. (%)	129 (6.8)	97 (7.4)
MDQ score, mean (*SD*)	4.9 (3.3)	2.8 (2.0)
Groups according to psychopathology		
Remitted anxiety and/or depressive disorder, no. (%)	560 (29.7)	433 (32.8)
Current anxiety and/or depressive disorder, no. (%)	1,328 (70.3)	886 (67.2)
Current anxiety disorder, no. (%)	456 (24.4)	17.2)
Current depressive disorder, no. (%)	326 (17.3)	221 (11.9)
Current anxiety and/or depressive disorder, no. (%)	546 (28.9)	346 (18.7)
Five factor personality scales of the NEO−FFI		
Neuroticism, mean (*SD*)	38.4 (8.1)	37.6 (8.3)
Extraversion, mean (*SD*)	35.7 (7.0)	35.5 (7.0)
Openness, mean (*SD*)	38.5 (5.9)	38.3 (5.9)
Agreeableness, mean (*SD*)	43.7 (5.2)	44.4 (5.0)
Conscientiousness, mean (*SD*)	40.9 (6.5)	41.6 (6.2)

Table 2.1: Characteristics of the Study Sample of NESDA Participants

Abbreviations:
BMI = Body Mass Index;
IDS-SR = Inventory of Depressive Symptomatology, self-report;
BAI = Beck Anxiety Inventory;
SSRI = Selective Serotonin Reuptake Inhibitor;
TCA = Tricyclic Antidepressant.

2.4.3 Predictors of Incidence of (Hypo)manic Symptoms

Results of the crude models showed significant effects for neuroticism, agreeableness, and conscientiousness on the incidence of (hypo)manic symptoms. In the adjusted models, high neuroticism and low agreeableness remained significantly related to the onset of (hypo)manic symptoms with HRs of 1.21 ($p = 0.03$, 95% CI [1.02, 1.43]) for neuroticism, and 0.74 ($p < 0.001$, 95% CI [0.64, 0.85]) for agreeableness. In the fully adjusted model, again, agreeableness was the only statistically, significant independent predictor, with an HR of 0.77 ($p = 0.001$, 95% CI [0.66, 0.89]) (see Table 2.1 and Figure 2.1B). In addition, when we used the traditional coding of incident cases (a history of [hypo]manic symptoms) for the MDQ, there were 62 incident cases versus 233 cases of slightly modified coding. However, the results were similar, with a multivariate-adjusted HR of 0.59 ($p < 0.001$, 95% CI [0.45, 0.77]) for agreeableness using the 62 incident cases and a HR of 0.77 ($p = 0.001$, 95% CI [0.66, 0.89]) using the 233 cases.

	Crude hazard ratio **[95% CI]**	***p* value**	Adjusted hazard ratio **[95% CI]∗**	***p* value**	Fully adjusted hazard ratio **[95% CI]∗∗**	***p* value**
CIDI (hypo)manic episode (n = 31/1,888; 1.6%)						
Neuroticism	2.08 [1.32, 3.30]	0.002	1.70 [1.03, 2.82]	0.04	1.29 [0.65, 2.54]	0.46
Extraversion	0.81 [0.56, 1.17]	0.26	0.92 [0.63, 1.36]	0.69	1.44 [0.90, 2.31]	0.13
Openness	1.02 [0.71, 1.46]	0.92	1.11 [0.77, 1.61]	0.57	1.14 [0.79, 1.64]	0.50
Agreeableness	0.49 [0.35, 0.68]	< 0.001	0.52 [0.37, 0.74]	< 0.001	0.54 [0.37, 0.80]	0.002
Conscientiousness	0.70 [0.50, 0.98]	0.04	0.79 [0.56, 1.12]	0.18	0.91 [0.61, 1.36]	0.64
MDQ (hypo)manic symptoms (n = 233/1,319; 17.7%)						
Neuroticism	1.33 [1.14, 1.54]	< 0.001	1.21 [1.02, 1.43]	0.03	1.03 [0.81, 1.32]	0.79
Extraversion	0.89 [0.78, 1.02]	0.10	0.69 [0.83, 1.11]	0.58	1.15 [0.95, 1.38]	0.14
Openness	0.95 [0.83, 1.08]	0.40	1.05 [0.91, 1.21]	0.47	1.07 [0.93, 1.23]	0.38
Agreeableness	0.69 [0.60, 0.78]	< 0.001	0.74 [0.64, 0.85]	< 0.001	0.77 [0.66, 0.89]	0.001
Conscientiousness	0.85 [0.74, 0.97]	0.01	0.81 [0.78, 1.02]	0.09	0.94 [0.80, 1.01]	0.40

Table 2.2: Personality and the Risk of an Incident (Hypo)Manic Episode or Symptoms in Patients with Anxiety and/or Depressive Disorder.
Personality traits Z scores were used for Cox regression analysis.
∗ Data were adjusted for age, gender, education, and current depressive and anxiety disorders at baseline.
∗∗ Data were additionally adjusted for severity of depression and anxiety, childhood trauma, alcohol dependence, and the four remaining personality traits in the model.

2.5 Discussion

The main goal of the current study was to determine which personality traits are independently associated with the development of a (hypo)manic episode or (hypo)manic symptoms within a group of patients who were initially diagnosed with unipolar depression and anxiety disorders. We found that low agreeableness was a personality-related risk factor that could anticipate the development of a (hypo)manic episode or associated symptoms.

Our results are partly in line with previous studies. A link between low agreeableness and BD was found in a large prospective study[25] and two cross-sectional studies[16, 20].

Our finding that depressed and anxious patients with low agreeableness are at risk of developing (hypo)mania has potential clinical implications. Identifying those patients at increased risk of BD early on would allow preventative intervention. BD is often missed or misdiagnosed by clinicians; this is illustrated by an average treatment delay of up to 10 years after the first major mood episode[40]. Although the criteria for classifying (hypo)mania in patients with BD and unipolar depressive disorder are very clear, it is often not obvious in clinical practice. BD patients start often with predominantly depressive episodes, which are usually later followed by (hypo)manic episodes. (Hypo)manic episodes are regularly unnoticed or not mentioned by patients. An unjustified diagnosis of unipolar disorder can have major disadvantages such as inadequate pharmacological treatment. Inadequate pharmacological treatments are associated with an increased risk of recurrence, non-response, longer illness duration, and possible induction of (hypo)mania[41]. Therefore, it is important to be able to identify BD and distinguish it from unipolar disorder. Specific personality traits may be warning signs of BD, in addition to clinical characteristics such as multiple brief depressed episodes, a lack of response to antidepressants, and a family history of BD[41]. A patient assessment that reveals high emotional instability and a tendency to disagree, compete, and be suspicious could also indicate a heightened risk. Likewise, a lack of being cooperative, trusting, and amiable is a sign of low agreeableness[42]. Our findings are consistent with the idea that BD patients tend to be less agreeable, which might be associated with less willingness to follow advice. Accordingly, euthymic BD groups are more likely to oppose advice given in a computerized goal-directed task after a positive mood induction[43] compared with remitted unipolar and healthy controls. In line with this, BD patients tend to show more anti-social behavior (such as aggression and inappropriate anger attacks) compared with depressive patients and healthy controls[44]. Low agreeableness might also be associated with anti-social behavior. Moreover, BD patients experience extensive emotional instability during their mood episodes and also in between the episodes in their euthymic state. Earlier studies have shown that BD patients more often use maladaptive strategies such as rumination and dampening compared with healthy controls. These maladaptive strategies may adversely impact mood symptoms and severity[45], and were associated with higher scores on maladaptive personality traits (such as neuroticism) and lower scores on adaptive personality traits (such as agreeableness and openness). Our findings match those of previous studies and suggest that such characteristics may signal a risk of BD, even in the euthymic phase.

In contrast to earlier findings, we did not confirm that high neuroticism was an independent predictor of the development of (hypo)mania in our current study; this association

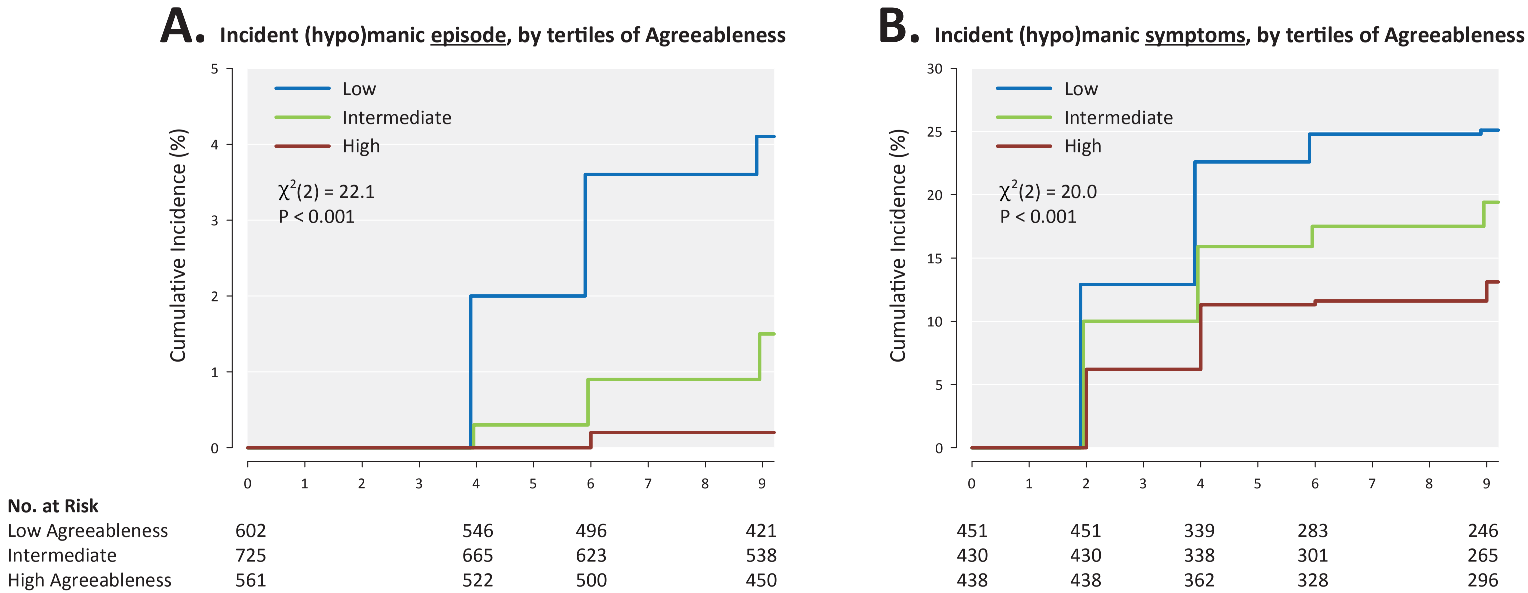


Figure 2.1: (A) Kaplan-Meier curves of incident (hypo)manic episode by tertiles of agreeableness. The cumulative incident of end points is shown in 1888 patients based on (hypo)manic episodes (CIDI). (B) Kaplan-Meier curves of incident (hypo)manic symptoms by tertiles of agreeableness. The cumulative incident of end points is shown in 1319 patients based on (hypo)manic symptoms (MDQ); p-value by log-rank (Mantel-Cox) test.

has been found in several cross-sectional[16, 17, 18, 19, 20] and three predictive studies[14, 25, 26]. In these studies, higher neuroticism correlated with baseline depression symptoms or predicted future depression symptoms, but did not predict future (hypo)manic episode or symptoms. The core features of neuroticism are associated with depression; therefore, it was important for us to adjust for the severity of depression symptoms in the current study. In our sample, neuroticism and the IDS-SR scores were strongly intercorrelated. Adjusting for the severity of depression explains the lack of a significant association with neuroticism in our current analyses.

Another previous finding that we did not confirm was the association between high extraversion and BD, which was found in one predictive study, one conversion study[14, 15], and several cross-sectional studies[18, 21, 22, 23, 24]. Extraversion was mainly related to (hypo)manic symptoms. Although we were not able to differentiate between BDI and BDII, it is plausible that a substantial number of incident cases in our study were BDII. Results from an earlier predictive study[46] indicated that higher neuroticism and lower extraversion were particularly predictive of BDII rather than BDI incident cases. Personality traits could be a distinguishing feature of these two subtypes.

The current study has several strengths over previous studies. The most important strengths are the large sample size and the long follow-up period (the longest to date). Moreover, we took potential confounders such as the presence and severity of depression and anxiety into account. We also assessed incidence of (hypo)mania using a validated instrument and excluded prevalent disorders or symptoms in the subsequent analyses. Unlike the present study, other prospective studies were population-based or conducted with samples of patients already diagnosed with BD at baseline[14, 25, 26]; therefore, these studies could not examine the risk factors for BD development since they already included BD patients at baseline.

The study of[15] is most comparable to our study in terms of design, because their participants were diagnosed with a depressive disorder at baseline, were followed for 5 years, and analyses were adjusted for depression severity. However, our study has important differences. For instance,[15] used the life chart and SCAN interviews to identify BD, and did not exclude prevalent BD patients at baseline. In addition, they only assessed two personality traits (extraversion and neuroticism), and had a smaller sample size ($n = 301$). All in all, our findings corroborate findings from most previous studies and suggest that low agreeableness is a personality-related risk factor that may predict the development of a (hypo)manic episode.

There are some limitations to our study. The exclusion of BD patients based on the CIDI was only possible at the 2-year follow-up because the BD section of the CIDI was not conducted at baseline. However, during the initial screening for participation, patients with a clinical diagnosis of BD were excluded, and we also applied a lag-time analysis which excluded the first 2 years of observation. This resulted in a relatively small sample of patients who had experienced a (hypo)manic episode. Although the attrition in the number of participants over 9 years follow-up was limited, drop-out may not have been at random, leading to potential selective attrition in those with (hypo)manic symptoms compared with participants from the other group, introducing the risk of survival bias. In addition, despite the time-lag analysis, diagnoses of BD, cyclothymia, or subsyndromal symptoms might have been missed at baseline. Another possible limitation is that the severity of depression or anxiety disorder at baseline might have influenced the personality assessment. An earlier analysis of the current NESDA study[47] examined the influence of depressive and anxiety disorders on personality score, as both mood disorders and the Big Five traits were assessed with a time interval of 4 years. Their results showed that depressive and anxiety disorders both increased neuroticism scores. Extraversion and conscientiousness scores were influenced by depressive disorder, but not by anxiety disorder. Most importantly, agreeableness and openness were influenced by neither. Moreover, data on the Big Five personality characteristics were available but information about formal DSM-IV diagnoses of personality disorders was not. Since many participants suffered from a current mood disorder at baseline, DSM diagnoses of personality disorders cannot be reliably ascertained. Another limitation is the possibility of construct overlap between low agreeableness and hypomania, as low agreeableness could be an expression of over-confidence and following your own goals instead of considering what others want or need[48]. Finally, although we could adjust for the most important confounders, data on the family history of BD were missing.

In summary, we found that low agreeableness increased the risk of (hypo)manic episodes and the symptoms thereof. Clinicians must be aware of these personality characteristics in order to recognize the early signs (usually depression) in patients with depressive and anxiety disorders. Future prospective studies investigating the relationship between personality traits and people at high risk for the development of (hypo)mania (e.g., first-line relatives or offspring of BD patients) are needed to confirm and deepen our understanding of this relationship. The potential benefit of psychotherapeutic interventions to treat low agreeableness in patients at risk of BD also warrants further attention.

Bibliography

1. Perlis RH et al. *Revisiting Depressive-Prone Bipolar Disorder: Polarity of Initial Mood Episode and Disease Course Among Bipolar I Systematic Treatment Enhancement Program for Bipolar Disorder Participants*. 2005.
2. Bauer M and Pfennig A. "Epidemiology of bipolar disorders". In: *Epilepsia* 46 Suppl 4 (2005), pp. 8–13.
3. Merikangas KR et al. "Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative". In: *Arch. Gen. Psychiatry* 68.3 (2011), pp. 241–251.
4. Gilman SE, Dupuy JM, and Perlis RH. "Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on Alcohol and Related Conditions". In: *J. Clin. Psychiatry* 73.6 (2012), pp. 829–836.
5. Vai B, Bertocchi C, and Benedetti F. *Cortico-limbic connectivity as a possible biomarker for bipolar disorder: where are we now?* 2019.
6. Dom G and Moggi F, eds. *Co-occurring Addictive and Psychiatric Disorders: A Practice-Based Handbook from a European Perspective*. Vol. 8. Berlin, Heidelberg: Springer Berlin Heidelberg, 2015, pp. 163–163.
7. Perlis RH, Brown E, Baker RW, and Nierenberg AA. "Clinical features of bipolar depression versus major depressive disorder in large multicenter trials". In: *Am. J. Psychiatry* 163.2 (2006), pp. 225–231.
8. Zaninotto L et al. "A meta-analysis of temperament and character dimensions in patients with mood disorders: Comparison to healthy controls and unaffected siblings". In: *J. Affect. Disord.* 194 (2016), pp. 84–97.
9. Angst J, Frey R, Lohmeyer B, and Zerbin-Rüdin E. "Bipolar manic-depressive psychoses: results of a genetic investigation". In: *Hum. Genet.* 55.2 (1980), pp. 237–254.
10. Kwapil TR et al. "A longitudinal study of high scorers on the hypomanic personality scale". In: *J. Abnorm. Psychol.* 109.2 (2000), pp. 222–226.

11. Carver CS. “Negative affects deriving from the behavioral approach system”. In: *Emotion* 4.1 (2004), pp. 3–22.
12. Costa Jr PT and McCrae RR. “Domains and facets: hierarchical personality assessment using the revised NEO personality inventory”. In: *J. Pers. Assess.* 64.1 (1995), pp. 21–50.
13. Akiskal HS et al. “The distinct temperament profiles of bipolar I, bipolar II and unipolar patients”. In: *J. Affect. Disord.* 92.1 (2006), pp. 19–33.
14. Sparding T, Pålsson E, Joas E, Hansen S, and Landén M. “Personality traits in bipolar disorder and influence on outcome”. In: *BMC Psychiatry* 17.1 (2017), p. 159.
15. Bukh JD, Andersen PK, and Kessing LV. “Personality and the Long-Term Outcome of First-Episode Depression: A Prospective 5-Year Follow-Up Study”. In: *J. Clin. Psychiatry* 77.6 (2016), e704–10.
16. Quilty LC, Sellbom M, Tackett JL, and Bagby RM. “Personality trait predictors of bipolar disorder symptoms”. In: *Psychiatry Res.* 169.2 (2009), pp. 159–163.
17. Solomon DA et al. “Personality traits in subjects with bipolar I disorder in remission”. In: *Journal of Affective Disorders* 40.1 (1996), pp. 41–48. ISSN: 01650327.
18. Jylhä P et al. “Differences in neuroticism and extraversion between patients with bipolar I or II and general population subjects or major depressive disorder patients”. In: *Journal of Affective Disorders* 125.1 (2010), pp. 42–52. ISSN: 0165-0327.
19. Vinberg Christensen M and Vedel Kessing L. “Do personality traits predict first onset in depressive and bipolar disorder?” In: *Nordic Journal of Psychiatry* 60.2 (2006), pp. 79–88. ISSN: 0803-9488, 1502-4725.
20. Murray G, Goldstone E, and Cunningham E. “Personality and the predisposition(s) to bipolar disorder: heuristic benefits of a two-dimensional model”. In: *Bipolar Disord.* 9.5 (2007), pp. 453–461.
21. Hirschfeld RM, Klerman GL, Keller MB, Andreasen NC, and Clayton PJ. “Personality of recovered patients with bipolar affective disorder”. In: *J. Affect. Disord.* 11.1 (1986), pp. 81–89.
22. Cloninger CR, Przybeck TR, and Svrakic DM. “The Tridimensional Personality Questionnaire: U.S. Normative Data”. In: *Psychol. Rep.* 69.3 (1991), pp. 1047–1057.
23. Akiskal HS, Hirschfeld RMA, and Yerevanian BI. “The Relationship of Personality to Affective Disorders: A Critical Review”. In: *Arch. Gen. Psychiatry* 40.7 (1983), pp. 801–810.
24. Bagby RM et al. “Relationship between the five-factor model of personality and unipolar, bipolar and schizophrenic patients”. In: *Psychiatry Res.* 70.2 (1997), pp. 83–94.
25. Barnett JH et al. “Personality and bipolar disorder: dissecting state and trait associations between mood and personality”. In: *Psychol. Med.* 41.8 (2011), pp. 1593–1604.
26. Lozano BE and Johnson SL. “Can personality traits predict increases in manic and depressive symptoms?” In: *J. Affect. Disord.* 63.1-3 (2001), pp. 103–111.

27. Du N, Zhou Y.-l, Zhang X, Guo J, and Sun X.-l. “Do some anxiety disorders belong to the prodrome of bipolar disorder? A clinical study combining retrospective and prospective methods to analyse the relationship between anxiety disorder and bipolar disorder from the perspective of biorhythms”. In: *BMC Psychiatry* 17.1 (2017).

28. Penninx BWJH et al. “The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods”. In: *Int. J. Methods Psychiatr. Res.* 17.3 (2008), pp. 121–140.

29. Wittchen H.-U et al. “Cross-cultural Feasibility, Reliability and Sources of Variance of the Composite International Diagnostic Interview (CIDI)”. In: *British Journal of Psychiatry* 159.5 (1991), pp. 645–653.

30. Lecrubier Y et al. “The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI”. In: *European Psychiatry* 12.5 (1997), pp. 224–231.

31. Hirschfeld RM et al. “Development and Validation of a Screening Instrument for Bipolar Spectrum Disorder: The Mood Disorder Questionnaire”. In: *American Journal of Psychiatry* 157.11 (2000), pp. 1873–1875.

32. Boschloo L et al. “The Mood Disorder Questionnaire (MDQ) for detecting (hypo)manic episodes: Its validity and impact of recall bias”. In: *Journal of Affective Disorders* 151.1 (2013), pp. 203–208.

33. Hirschfeld RMA. “The Mood Disorder Questionnaire”. In: *The Primary Care Companion For CNS Disorders* 4.1 (2002).

34. Saucier G. “Replicable Item-Cluster Subcomponents in the NEO Five-Factor Inventory”. In: 70 (1998), pp. 263–276. issn: 0022-3891.

35. Wittchen H.-U. “Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): A critical review”. In: *Journal of Psychiatric Research* 28.1 (1994), pp. 57–84. issn: 0022-3956.

36. Boschloo L et al. “Predictors of the Onset of Manic Symptoms and a (Hypo)Manic Episode in Patients with Major Depressive Disorder”. In: *PLoS ONE* 9.9 (2014). Ed. by Potash JB, e106871.

37. Rush AJ, Gullion CM, Basco MR, Jarrett RB, and Trivedi MH. “The Inventory of Depressive Symptomatology (IDS): psychometric properties”. In: *Psychological Medicine* 26.3 (1996), pp. 477–486.

38. Beck AT, Epstein N, Brown G, and Steer RA. “An inventory for measuring clinical anxiety: Psychometric properties.” In: *Journal of Consulting and Clinical Psychology* 56.6 (1988), pp. 893–897.

39. Wiersma JE et al. “The Importance of Childhood Trauma and Childhood Life Events for Chronicity of Depression in Adults”. In: 70 (2009), pp. 983–989. issn: 0160-6689.

40. Drancourt N et al. “Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment”. In: *Acta Psychiatr. Scand.* 127.2 (2013), pp. 136–144.

41. Ghaemi SN, Boiman EE, and Goodwin FK. “Diagnosing Bipolar Disorder and the Effect of Antidepressants. A Naturalistic Study”. In: 61 (2000), pp. 804–808. issn: 0160-6689.

42. Chapman BP. “Bandwidth and Fidelity on the NEO-Five Factor Inventory: Replicability and Reliability of Item Cluster Subcomponents”. In: *Journal of Personality Assessment* 88.2 (2007), pp. 220–234.

43. Mansell W and Lam D. ““I Won’t Do What You Tell Me!”: Elevated mood and the assessment of advice-taking in euthymic bipolar I disorder”. In: *Behaviour Research and Therapy* 44.12 (2006), pp. 1787–1801.

44. Mammen OK, Pilkonis PA, Chengappa KNR, and Kupfer DJ. “Anger attacks in bipolar depression: predictors and response to citalopram added to mood stabilizers. Predictors and Response to Citalopram Added to Mood Stabilizers”. In: *J. Clin. Psychiatry* 65.5 (2004), pp. 627–633. ISSN: 0160-6689.

45. Dodd A, Lockwood E, Mansell W, and Palmier-Claus J. “Emotion regulation strategies in bipolar disorder: A systematic and critical review”. In: *J. Affect. Disord.* 246 (2019), pp. 262–284.

46. Kim B, Lim J.-H, Kim SY, and Joo YH. “Comparative Study of Personality Traits in Patients with Bipolar I and II Disorder from the Five-Factor Model Perspective”. In: *Psychiatry Investigation* 9.4 (2012), p. 347. ISSN: 1738-3684, 1976-3026.

47. Karsten J et al. “The state effect of depressive and anxiety disorders on big five personality traits”. In: *J. Psychiatr. Res.* 46.5 (2012), pp. 644–650.

48. Sukenik S, Reizer A, and Koslovsky M. “Direct and Indirect Effects of Agreeableness on Overconfidence”. In: *Journal of Individual Differences* 39.3 (2018), pp. 174–181.

CHAPTER 3

Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder

Mesbah, R., de Bles, N., Rius-Ottenheim, N., van der Does, A. J. W., Penninx, B. W. J. H., van Hemert, A. M., de Leeuw, M., Giltay, E. J., & Koenders, M. (2021). Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder. *Depression and Anxiety*, 38(6), 671-681. DOI: 10.1002/da.23137

Abstract

Introduction
Feelings of anger and irritability are prominent symptoms of bipolar disorder (BD) that may occur during (hypo)manic, depressive and, especially, during mixed mood states. We aimed to determine whether such constructs are associated with (the conversion to) BD in subjects with (a history of) unipolar depression.

Methods
Data were derived from the depressed participants of Netherlands Study of Depression and Anxiety with 9 years of follow-up. (Hypo)mania was ascertained using the Composite International Diagnostic Interview at 2, 4, 6, and 9 years follow-up. Cross-sectionally, we studied the association between prevalent (hypo)mania and anger related constructs with the 'Spielberger Trait Anger subscale', the 'Anger Attacks' questionnaire, the cluster B personality traits part of the 'Personality Disorder Questionnaire', and 'aggression reactivity'. Prospectively, we studied whether aggression reactivity predicted incident (hypo)mania using Cox regression analyses.

Results
Cross-sectionally, the bipolar conversion group (n = 77) had significantly higher scores of trait anger and aggression reactivity, as well as a higher prevalence on 'anger attacks', 'anti-social traits', and 'borderline traits' compared to current (n = 349) as well as remitted (n = 1,159) depressive patients. In prospective analyses in 1,744 participants, aggression reactivity predicted incident (hypo)mania (n = 28), with a multivariate-adjusted hazard ratio of 1.4 (95% CI: 1.02-1.93; $p = 0.037$).

Conclusions
Anger is a risk factor for conversion from unipolar depression to BD. In addition, patients who converted to BD showed on average more anger, agitation and irritability than people with (a history of) unipolar depression who had not converted.

3.1 Introduction

Bipolar disorder (BD) is a severe and debilitating mood disorder, characterised by (hypo)manic and depressive episodes[1]. Most patients with BD have experienced one or more episodes of depression prior to the onset of (hypo)mania[2, 3], and as a consequence are initially diagnosed with an unipolar depression. Since the treatment for unipolar depression is different from BD and may instigate (hypo)mania[4], earlier detection of a vulnerability to BD would benefit these patients. Moreover, risk factors for the conversion to BD may yield anchor points for (psychological) interventions, for early recognition and appropriate treatment.

Previous studies showed that a parental history of BD, more severe depression, comorbid psychotic symptoms, childhood trauma and atypical symptoms of depression were risk factors for a conversion from unipolar to BD[3, 5, 6]. Irritability and anger in unipolar depression appeared to be a robust clinical marker of undiagnosed or subthreshold bipolar disorder, or so-called bipolar spectrum illness[7, 8]. It is important to examine the association between anger and BD, because of its impact on the patient and family and loved ones. Knowing there is an association can help us to target treatment. It is also important to properly investigate whether experiencing irritability/anger would have predictive value in the development of BD.

Anger can be divided into feelings and expressions. The feeling of anger involves different constructs, encompassing: trait- and state anger[9, 10]. Trait anger is defined by the constant tendency to experience anger upon the slightest provocation. It is a chronic condition that is intertwined in one's personality. A high level of anger can be a personality trait[11]. State anger is defined as the temporary psychological, emotional feeling at a particular time and situation that can vary in intensity from mild irritation to intense fury and rage[12]. These angry feelings could lead to the expression of anger including anger attacks and aggression. Attacks are spells of anger of a sudden surge of autonomic arousal with symptoms such as tachycardia, sweating, flushing, and a feeling of being out of control. They are experienced as uncharacteristic and may occur in inappropriate situations[13]. Anger attacks are associated with verbal and physical aggression, which in turn can cause social avoidance in order to prevent a future anger attack and has certainly a negative impact on interpersonal relations[14]. All emotional states of anger, agitation and irritability will be referred to as anger in the current paper.

Anger might be part of emotion regulation problems and it has been hypothesized that heightened emotionality is an enduring characteristic of BD[15]. This suggests that people with BD experience more intense and more frequently fluctuating negative and positive emotions (apart from their mood episodes). This might increase their risk of developing mood episodes. Most previous studies found cross-sectional associations between anger and bipolarity[16, 17, 18, 19, 20]. In one prospective study (255 BD, 85 non-BP psychopathology and 84 healthy controls) BD patients reported persistently higher scores on self-report questionnaires on anger and feelings of aggression compared to psychiatric and healthy controls across a four-year follow-up[21]. There are indications that people with BD show stronger emotional reactivity compared to healthy controls on self-report questionnaires[22, 23], or specifically report more anger and frustration during euthymic states[24, 25], but contradictory findings have been reported as well[26].

Emotional instability in BD is often mistaken for comorbid personality disorder, since this is such a core characteristic of especially cluster B personality disorders. Ecological momentary assessments (EMA) studies have shown that BD patients in remission report more overall negative affect[27, 28] and more fluctuations in both negative and positive emotionality compared to healthy controls[29]. Earlier cross-sectional studies have found that some of the symptoms of BD (e.g. irritability, anger and emotional instability) overlap with personality disorders such as borderline personality disorder and antisocial personality disorder[30, 31]. In total, 44% of patients diagnosed with borderline personality disorder were found to meet strict diagnostic criteria for BD[32]. Moreover, 55% of newly diagnosed BD patients (without comorbid personality disorder) showed signs of juvenile antisocial behaviour in a retrospective study[33]. These findings suggest that borderline and antisocial personality disorders have construct overlap with BD. Especially affective instability and impulsivity were traits that may link BD to personality disorders[34].

In sum, the majority of the studies have shown a relation between BD and emotional instability, and specifically of anger, also in stable periods. In the current study, we investigated whether patients who converted to BD showed more feelings of anger, irritability and antisocial and borderline personality traits than people with (a history of) unipolar depression who did not convert. Second, we aimed to determine whether increased aggression reactivity increases the risk of conversion from depression to BD.

3.2 Methods

3.2.1 Study sample

Data were derived from the Netherlands Study of Depression and Anxiety (NESDA) with measurement points at baseline and at the 2-, 4-, 6-, and 9-year follow-up. NESDA is an ongoing longitudinal cohort study, consisting of 2,981 participants (18-65 years). Participants were recruited at baseline from community care (19%), primary care (54%), and specialized mental health care (27%) in the Netherlands. Individuals included in the NESDA study were participants with current or remitted depressive disorders and/or comorbid anxiety. The control group consisted of participants without lifetime psychiatric disorders. Exclusion criteria included (1) the presence of other psychiatric disorders (e.g., psychotic, obsessive-compulsive, bipolar, or severe addiction disorder) and (2) not being fluent in Dutch. Participants gave written informed consent before enrolment, and ethical approval was granted by all ethical committees of participating universities (VU University Medical Center, Leiden University Medical Center and University Medical Center Groningen). A detailed description of NESDA is given elsewhere[35]. Specially trained research staff administered the diagnostic interviews using the Composite International Diagnostic Interview (CIDI, version 2.1) to assess remitted or current depressive disorders and incidents of (hypo)mania which is indicative for BD. In the current study, we analysed data cross-sectionally and prospectively (with survival analysis).

Cross-sectional analysis sample: data on anger related questionnaires (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger) were gathered only at the 4^{th} wave at 4-year follow-up. Therefore, we selected participants who completed the 4^{th} wave (n = 2,402; 80.6%) to examine the construct of anger cross-sectionally. Participants suffering from a remitted and current depressive disorder and BD patients who converted between baseline and 4 years of follow-up were included. In a previous NESDA study[36], healthy controls showed significantly less trait anger and had lowest prevalence of anger attacks compared with groups of depression with or without comorbid anxiety disorder. For this reason, healthy controls were excluded in the current study. Participants with missing data on questionnaires regarding (hypo)manic episodes, or on one of the anger-related questionnaires were excluded, resulting in a total sample of 1,585 (53.2%) of the 2,981 participants for the cross-sectional analyses (see Flowchart in Figure 3.1).

Prospective analysis sample: aggression reactivity questionnaire was the only measured anger related instrument at baseline. Therefore, aggression reactivity was used as the predictor for incident (hypo)mania during the 9 years of follow-ups. We included 1,744 (58.5%) of 2,981 participants, with remitted or current depressive disorder with at least one follow-up assessment (Figure 3.1).

3.2.2 Measures

Aggression reactivity. This questionnaire was used in prospective analysis as predictor and in cross-sectional as one of the anger-related constructs. It was measured with the aggression reactivity subscale of the Leiden Index of Depression Sensitivity - Revised (LEIDS-R)[37, 38]. The LEIDS-R contains 34 items with six subscales. Aggression Reactivity is one of these subscales and has six items (e.g. 'In a sad mood, I do more things that I will later regret'; 'When I feel bad, I feel like more breaking things'; 'In a sad mood I'm more bothered by aggressive thoughts'; 'When I feel down, I more easily become cynical or sarcastic'; 'When I feel sad, I do more risky things'; 'When feel down, I lose my temper more easily'). These items measure how people react in a sad mood. Items are answered on a 5-point Likert scale from 0-4, with total scores ranging from 0-24. The internal consistency (Cronbach's alpha) for the aggression reactivity subscale was 0.80 in the current NESDA sample.

CIDI (hypo)manic episodes. The Composite International Diagnostic Interview (CIDI; WHO version 2.1) is a comprehensive, fully standardized diagnostic interview to screen for mental disorders based on DSM-IV criteria. The CIDI was used to assess remitted or current depressive disorders in the preceding 6 months. Incident cases of (hypo)manic episodes, which were indicative of BD, were ascertained using the CIDI "bipolar" section. The CIDI has high interrater reliability, (BDI: $\kappa = 0.92$, BDII: $\kappa = 0.94$)[39] and is a valid instrument (diagnosis of a lifetime BD sensitivity 0.87 and specificity 0.89)[40] for yielding DSM-IV diagnoses.

Trait anger. Trait anger was assessed via the Dutch adaption of the Spielberger State-Trait Anger Scale (STAS)[41, 42] and was gathered at the 4th wave at 4-year follow-up. The STAS is divided into two subscales for state and trait anger, whereby only the latter was administered in the current study. Trait anger is described as anger proneness as a personality trait[43]. The trait anger scale is a 10-item, self-report questionnaire. Participants score items on a 4-point Likert scale from 1-4. The total sum score ranges from 10-40. Psychometric properties have shown good item correlations, high test-retest reliability, and high internal consistency values with Cronbach's alphas ranging from 0.75 to 0.91[41, 42]. The internal consistency (i.e., Cronbach's alpha) in our sample was 0.89.

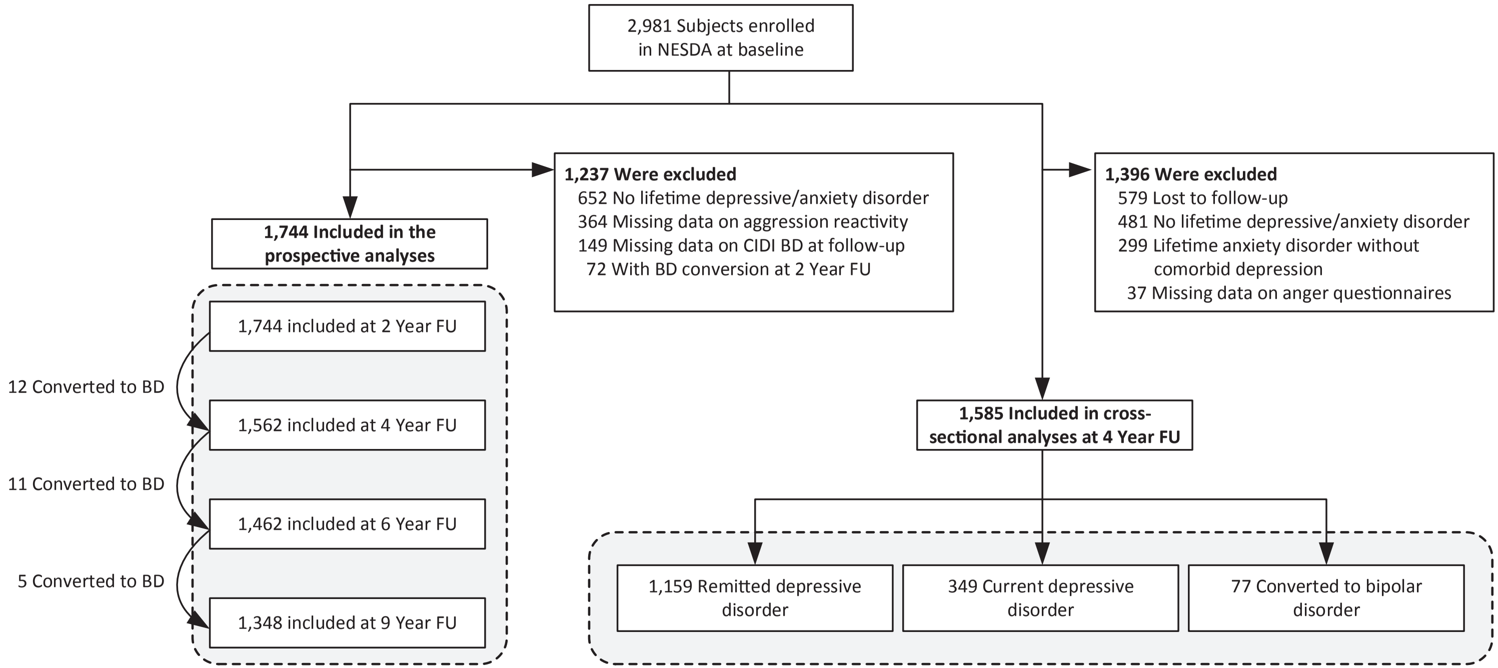


Figure 3.1: Flowchart of included participants in prospective and cross-sectional analyses.

Anger attacks. The Anger Attacks Questionnaire[14] is a self-rated instrument used to measure the presence or absence of anger attacks during the previous 6 months. It was measured at the 4th wave at 4-year follow-up. Anger attacks are sudden spells of anger inappropriate to the situation, accompanied by irritability, a sense of being out of control, and autonomic arousal symptoms[14]. To define who was experiencing anger attacks, the following criteria had to be met the previous 6 months: (1) irritability, (2) overreaction to minor annoyances, (3) inappropriate anger and rage directed at others, (4) incidence of at least one anger attack within the past month, and (5) presence of at least four or more of the following symptoms in at least one of the attacks: tachycardia, hot flashes, tightness of the chest, paraesthesia, dizziness, shortness of breath, sweating, trembling, panic, feeling out of control, feeling like attacking others, attacking physically or verbally, and throwing or destroying objects.

Cluster B personality traits. Antisocial behaviour was assessed with the Dutch adaptation of the Personality Disorder Questionnaire (PDQ-4)[44] and data was gathered at the 4th wave at 4-year follow-up. It was used to identify the key features or possible presence of a personality disorder. Items included in the PDQ-4 were adapted from the diagnostic criteria for personality disorders of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994). In the current study, a shortened version of the PDQ-4 with 37 dichotomous ('true'/'false') was assessed. Items were divided into three subcategories; borderline personality disorder (15 items; e.g. "I have difficulty controlling my anger or temper"); antisocial personality disorder (8 items; e.g. "I don't care if others get hurt so long as I get what I want") and antisocial behaviour before the age of fifteen (14 items; e.g. "I was considered a bully"). Based on items of the subscales for borderline and antisocial personality traits the presence or absence of these symptomatology and characteristics was assessed. The PDQ-4 has a high sensitivity and moderate specificity (Cronbach's alpha = 0.97)[45], and a test-retest reliability of 0.67[46].

Covariates. Sociodemographic covariates were self-reported age, gender, and level of education (in years). Lifetime DSM IV-based alcohol dependency and abuse and drug use were assessed using the CIDI. In addition, the severity of depression during the past week was assessed with the 30-item self-report Inventory of Depressive Symptomatology (IDS)[47]. Items were scored on a 4-point Likert scale (0-3) with total sum score ranges from 0 to 84 (only 28 of the 30 items are rated) The IDS had good internal reliability (Cronbach's alpha = 0.85). This is a 21-item self-report inventory with an internal consistency (Cronbach's alpha) of 0.92[48]. Comorbid current anxiety use was assessed with CIDI.

3.3 Statistical analyses

Sociodemographic and clinical characteristics were summarized according to CIDI using descriptive statistics. Missing values of BMI and smoking status were imputed with the respective values from the previous wave.

Cross-sectional analyses. The CIDI was used to assess remitted or current depressive disorders and incident (hypo)manic episodes in the previous two years for cross-sectional analysis at the 4^{th} wave at 4-year follow-up. Upon completing the CIDI, participants were categorized into one of the following two psychopathology groups: remitted- and current depression. In these two groups a number of participants had experienced a (hypo)manic episode between baseline and 4-year follow-up, thus being classified in the BD converted group. We used analysis of variance (ANOVA) to compare the mean levels of the continuous variables trait anger and aggression reactivity, and chi-squared tests were used to compare the prevalence of the dichotomous variables anger attacks, antisocial and borderline personality traits among the three psychopathology groups (i.e., remitted depression, current depression, converted BD group). Furthermore, analyses were repeated for marginal means, resulting from adjustment for gender, age, level of education, alcohol and drugs use, severity of depressive symptoms and comorbid anxiety disorder using analysis of covariance (ANCOVA) and multivariable logistic regression analyses, when appropriate. The results of these analyses were presented in forest plots.

Moreover, multivariate linear regression analysis was used to analyse all the individual items of all the anger constructs (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger). Individual items estimated betas (with error bars representing 95% CI) were summarized and presented in supplementary forest plots. These were sorted by the size of each estimated beta for each construct separately.

Prospective analyses. At baseline, patients with a self-reported or with a professionally reported primary clinical diagnosis of BD were excluded. As the BD section of the CIDI was not conducted at baseline, we applied a lag-time analysis of 2 years, excluding all incident cases of (hypo)manic cases based on the CIDI between baseline and 2-year follow-up. In 1,744 participants, 28 experienced CIDI-confirmed incident (hypo)mania during follow-up (between 2 and 9 years). Kaplan-Meier analysis was used to examine the relationship between baseline aggression reactivity and conversion to BD. Hazard ratios (HR) with 95% confidence intervals (CI) of conversion to BD were estimated by Cox proportional hazards models. The date of inclusion into the cohort was considered the baseline for each patient in the survival analysis. The primary endpoint consisted of all incident cases during the follow-up period, the survival time, and the diagnoses at each time point (based on the CIDI). All follow-up losses as well as patients who did not experience a (hypo)manic episode were censored. We estimated three models: (a) a crude model that did not include any covariates, (b) an adjusted model that included gender, age, and level of education, and (c) a fully adjusted model that also included alcohol dependency, severity of depression symptoms and comorbid anxiety disorder. We tested for a linear trend across tertiles of incidents of (hypo)mania.

Multivariable logistic and Cox regression analyses and ANCOVA were performed using IBM SPSS statistical software (version 25, IBM Corp). The analyses regarding individual items and forest plots were computed using the R statistical software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.r-project.org/). A two-sided p value was considered statistically significant at the 0.05 level.

3.3.1 ResultsCross-sectional results

Demographic and clinical characteristics on (hypo)manic episodes of wave 4 (at 4 years follow-up) are shown in Table 3.1. Participants (N = 1,585) were on average 46.3 years old (SD = 12.6) and 68.8% were female. There were 77 (4.9%) patients who had converted from unipolar depression to BD based on CIDI during the two through four year waves (Table 3.1). There were no notable differences found in the sociodemographic between the groups. Patients with current depressive disorder showed more severe symptoms of depression compared with the other two groups. The group of converted patients smoked more often and suffered more from alcohol dependency than the two other groups. These patients also used more benzodiazepines, selective serotonin reuptake inhibitors and psychotropic medication compared to other groups.

Significant differences were present in the crude model for all anger constructs among the 3 groups (all p's < 0.001). The between differences persisted the adjusted models in continuous variables (see forest plot in Figure 3.2) with (F (2, 1582) = 8.20, $p < 0.001$ for trait anger; F (2, 1456) = 5.61, $p = 0.004$ for aggression reactivity. In the adjusted models, patients who were converted had the highest marginal mean levels on trait anger and aggression reactivity in comparison with remitted patients (with a mean difference; (MD = 1.87, SE = 0.6, $p = 0.001$) for trait anger, and (MD = 1.76, SE = 0.5, $p = 0.001$) for aggression reactivity and current depressed patients (MD = 2.35, SE = 0.6, $p < 0.001$) for trait anger, (MD = 1.71, SE = 0.6, $p = 0.002$) for aggression reactivity.

Results of adjusted analysis in categorical variables (see forest plot in Figure 3.3) were also significant with $\chi 2$ (2) = 4.55, $p = 0.041$ for anger attacks; $\chi 2$ (2) = 5.12, $p = 0.02$ for antisocial personality traits; and $\chi 2$ (2) = 10.41, $p = 0.001$ for borderline personality traits. Furthermore, the converted group also had the highest prevalence of anger attacks (22.1%), antisocial personality traits (9.1%) and borderline personality traits (36.4%) compared to those with remitted and current depression.

Results of the individual items of constructs (Supplementary Figures 3.5-3.9) with estimated betas and 95% CI show that anger attack items measuring physical sensation and anger items were most strongly associated with (hypo)mania. Moreover, almost all the items of PDQ borderline personality disorder-subscale were statistically significantly associated with (hypo)mania, and were more prominently associated than the other anger constructs. It was also notable that specifically the items that measure impulsiveness were strongly associated, rather than items that measure anti-sociability such as bullying or harming other people.

Table 3.1: Baseline characteristics of the study sample.
Data are means (with standard errors in parentheses) or number of participants (with percentages in parentheses).
IDS-SR = Inventory of Depressive Symptomatology, self-report.

	Baseline characteristics (*N*=1,744)	**4 year (wave 4) characteristics (*N*=1,585)**		
		Remitted depressive disorder (n=1159)	Current depressive disorder (n=349)	Converted group bipolar disorder (n=77)
All Sociodemographic:				
Female sex, no. (%)	1,290 (68.3%)	796 (68.7%)	253 (72.5%)	41 (53.2%)
Age in years, mean (SD)	42.5 (12.6)	46.2 (12.7)	47.0 (12.3)	44.8 (11.2)
Education, in years, mean (SD)	12.1 (3.3)	12.7 (3.3)	12.2 (3.3)	12.2 (3.3)
Body mass index (BMI), in kg/m^2, mean (SD)	25.7 (5.1)	26.3 (5.0)	26.4 (5.5)	26.9 (5.7)
Smoking, no. (%)	737 (39.0%)	371 (32.0%)	129 (37.0%)	34 (44.2%)
Alcohol dependency, no. (%)	549 (29.1%)	75 (6.5%)	42 (12.0%)	11 (14.3%)
Clinical characteristics:				
Severity depression IDS-SR total score, mean (SD)	33.03 (2.45)	14.95 (9.79)	29.45 (12.63)	24.70 (13.55)
Medication use, no. (%)				
Benzodiazepines	335 (17.7%)	124 (10.7%)	86 (24.6%)	20 (26.0%)
Selective serotonin reuptake inhibitors	411 (21.8%)	186 (16.0%)	65 (18.6%)	17 (22.1%)
Tricyclic antidepressants	63 (3.3%)	30 (2.6%)	17 (2.9%)	5 (6.5%)
Other antidepressants	129 (6.8%)	64 (5.5%)	46 (13.2%)	8 (10.4%)
Antipsychotic	35 (1.5%)	11 (0.9%)	12 (3.4%)	9 (11.7%)
Mood stabilizers	54 (3.1%)	21 (1.8%)	19 (5.4%)	8 (10.4%)

CIDI diagnosis groups	n	Crude mean (95%CI)	Test (crude)	Adjusted mean (95%CI)	Test (adjusted)
Trait anger					
- Remitted depressive disorder	1159	15.57 (15.31–15.84)	F(2, 1582) = 30.5; P < .001	16.12 (15.84–16.39)	F(2, 1582) = 8.20; P < .001
- Current depressive disorder	349	17.19 (16.62–17.76)		15.63 (15.10–16.17)	
- Converted group BD	77	19.15 (17.68–20.62)		18.03 (17.00–19.03)	
Aggression reactivity					
- Remitted depressive disorder	1078	4.92 (4.67–5.17)	F(2, 1466) = 24.39; P < .001	5.26 (5.00–5.51)	F(2, 1456) = 5.61; P = .004
- Current depressive disorder	324	6.24 (5.72–6.75)		5.30 (4.80–5.80)	
- Converted group BD	67	7.92 (6.81–9.03)		7.01 (6.01–8.01)	

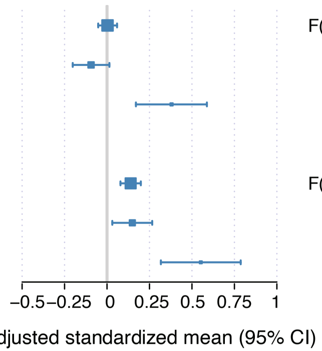


Figure 3.2: Forest plot showing the estimated marginal means (with 95% confidence intervals [CI]) of trait anger and aggression reactivity according to three diagnoses groups.

CIDI diagnosis groups	n (%)	Crude OR (95%CI)	Test (crude)	Adjusted OR (95%CI)	Test (adjusted)
Anger attacks					
- Remitted depressive disorder	99 (8.5%)	1.0 (ref)	χ^2 (2) = 26.3, P < 0.001	1.0 (ref)	χ^2 (2) = 4.55, P = 0.041
- Current depressive disorder	59 (16.9%)	2.18 (1.54–3.08)		1.55 (0,85–2,83)	
- Converted group BD	17 (22.1%)	3.03 (1.70–5.40)		1.98 (1.03–3.79)	
Antisocial personality traits					
- Remitted depressive disorder	15 (1.3%)	1.0 (ref)	χ^2 (2) = 19.1, P < 0.001	1.0 (ref)	χ^2 (2) = 5.12, P = 0.02
- Current depressive disorder	14 (4.0%)	3.19 (1.52–6.67)		1.82 (0.72–4.5)	
- Converted group BD	7 (9.1%)	7.63 (3.01–19.31)		3.5 (1.22–10.04)	
Borderline personality traits					
- Remitted depressive disorder	106 (9.1%)	1.0 (ref)	χ^2 (2) = 87.5, P < 0.001	1.0 (ref)	χ^2 (2) = 10.41, P = 0.001
- Current depressive disorder	93 (26.6%)	3.61 (2.65–4.92)		1.61 (0.93–2.78)	
- Converted group BD	28 (36.4%)	5.68 (3.42–9.41)		3.02 (1.65–5.53)	

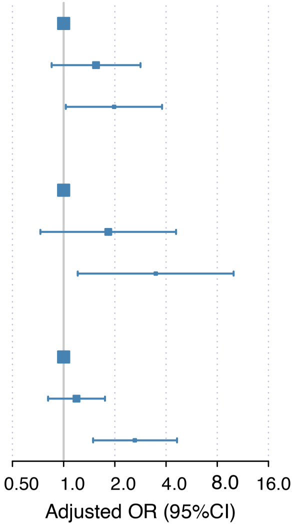
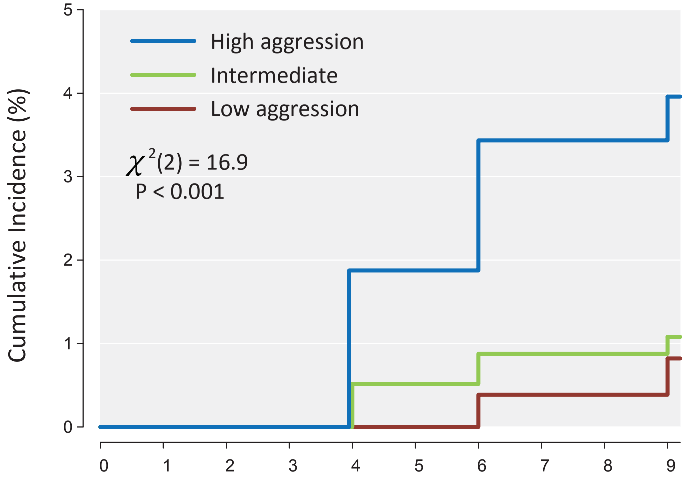


Figure 3.3: Forest plot showing (adjusted) odds ratios of anger attacks, antisocial and borderline personality traits according to three diagnoses groups. The adjusted analyses were adjusted for gender, age, level of education, alcohol dependency, drugs use, severity of depressive symptoms and comorbid anxiety disorder.



No. at Risk

Low aggression	590	546	517	461
Intermediate	623	583	548	496
High aggression	525	480	441	367

Figure 3.4: Kaplan-Meier curves of incident (hypo)mania according to tertiles of aggression reactivity. P value by log-rank (Mantel-Cox) test.

Table 3.2: Tertiles of aggression reactivity as a predictor of incident of (hypo)mania in sample of patients with depression and/or anxiety disorder.
Data obtained by an analysis of variance for trend, linear term.
*Adjusted for gender, age, level of education.
** Additionally adjusted for alcohol dependence and severity of depression symptoms

	Tertiles of aggression reactivity scores			**P-value for**
	Lower	**Intermediate**	**Higher**	**Trend#**
Participants, No.	590	623	525	
Cases, NO. (%)	4 (0.7%)	6 (1.0%)	18 (3.4%)	
Hazard ratio (95% confidence interval):				
Crude	1.0 (ref)	1.41 (0.40-4.99)	5.27 (1.79-15.6)	< 0.001
Adjusted*	1.0 (ref)	1.37 (0.39-4.88)	4.87 (1.63-14.6)	< 0.001
Fully adjusted model**	1.0 (ref)	1.34 (0.37-4.69)	4.63 (1.54-13.9)	0.037
	Continuous aggression reactivity (z-value)			**P-value**
Hazard ratio (95% confidence interval):				
Crude	1.84 (1.41-2.41)	< 0.001		
Adjusted*	1.78 (1.36-2.35)	< 0.001		
Fully adjusted model**	1.4 (1.02-1.93)	0.037		

3.4 Prospective results

Baseline characteristics are summarized in Table 3.1. The subjects at baseline (n = 1,744) were on average 42.5 years of age (SD = 12.6) and were predominantly female (68.3%). The sample consisted of 560 (29.7%) patients with remitted depressive and/or anxiety disorder and 1.328 (70.3%) patients with a current depressive and/or anxiety disorder. Based on CIDI 28 cases of (hypo)manic episodes were identified, signalling conversion to BD, from 2 through 9 years of follow-up. Relatively smaller number of incident cases of (hypo)mania in prospective analysis compared with cross-sectional analysis (28 versus 77) is due to the exclusion of all the cases between baseline and 2 years of follow-up in prospective analysis in order to exclude all prevalent cases from the prospective analysis.

Kaplan-Meier analysis of survival with the incident (hypo)manic episode as outcome showed that patients with higher levels of aggression reactivity had higher conversion rates compared to patients with lower levels of aggression reactivity (Figure 3.4). This association is also displayed in Table 3.2; showing that, compared to patients in the lower tertile of aggression reactivity (low is reference with HRs of 1 and intermediate with HRs of 1.34), those in the top tertile had a higher rate (HRs of 4.63) of incident cases of (hypo)mania. In the fully adjusted model, aggression reactivity was a significant predictor, with an HRs 1.4 (95% confidence interval, 1.02-1.93; P = 0.037) per 1-SD increase in aggression reactivity.

3.5 Discussion

The purpose of this study was first to examine the association of different constructs of anger with BD; and second to determine the predictive role of aggression reactivity in conversion to BD. Our study demonstrated a strong and consistent finding in the prospective as well as in the cross-sectional analyses. We found that higher levels of anger in all its variants were consistently associated with bipolarity versus those with (a history of) unipolar depression. Secondly, we found that aggression reactivity was predictive of conversion to BD.

Cross-sectionally, all the different constructs of anger and affective instability (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger) showed consistent associations, with the strongest association and highest prevalence in the converted group in comparison to the remitted and current depression groups. These results were in line with previous findings showing that BD patients scored higher on anger-related measures[20, 24] in comparison to unipolar depressed groups.

Regarding our prospective findings, we found that aggression reactivity was a risk factor for the conversion to BD in persons with (a history of) unipolar depression. Although two earlier prospective studies[21, 24] showed that feelings of anger were more frequent during the follow-up waves in BD patients in comparison with subjects with other psychiatric disorders and healthy controls, we are not aware of previous studies that examined the predictive value of an anger construct in relation to conversion to BD.

Affective instability and dysregulation in general seem to be distinctive factors for BD compared to unipolar depression in the current sample, since our results show that both antisocial- and borderline personality traits were more prevalent in the BD conversion group than in the currently depressed and remitted unipolar depression group. Results were most striking for the borderline traits, which is in line with previous findings showing that emotional instability is a core characteristic in both BD and borderline personality disorder.[32] suggest that the current classification may fail to differentiate between the two disorders considering the complexity and heterogeneity within these patient groups and that perhaps borderline and bipolar might be the two extremes of the same spectrum[32]. Additionally, a longitudinal study showed that comorbid borderline and antisocial personality traits predicted the risk of aggression in BD, while controlling for potential confounding factors[49].
Whether emotion regulation problems are more characteristic for BD than unipolar depression is unclear, since the few studies into this topic had contradicting results[50, 51]. We might carefully conclude, based on the current and previous findings, that especially anger and aggression dysregulation are the most distinct affective characteristics for BD when compared to unipolar depression. One important explanation for this finding might be the occurrence of mixed mood states. Although results are not fully conclusive, agitated depression or mixed depression (i.e., depressed episodes with the simultaneous presence of several manic symptoms, like irritability) in unipolar depression might be one of the early signs of conversion to BD since mixed episodes are more prevalent in BD[52]. However, it is unclear to what extent the current and previous findings are associated with the increased occurrence of mixed mood states in BD patients.

Another potential explanation for the more distinct problems in regulation of anger in BD patients compared to unipolar depression patients might reside in differences in emotion regulation styles. Although most dysfunctional emotion regulation styles are comparable between BD and unipolar depression patients (e.g., rumination and catastrophizing)[53, 54] there are indications for important differences. Both on the cognitive and behavioural levels, BD patients seem to have the tendency to upregulate activated mood states. For instance,[55] showed that positive appraisal about activated states predicted BD (in a sample with BD, unipolar depression and healthy controls). BD patients also seem to have more extreme positive self-relevant appraisals of the feelings of activation than healthy controls and unipolar depressed patients[56, 57]. Additionally, at least a subgroup of the bipolar patients are more likely to engage in stimulating and activating behaviour (that potentially induces a (hypo)manic episodes). Although previous studies focussed specifically on activated states such as happiness or euphoria, anger can also be considered as an activated mood state as well.

Feelings of anger might be an important target for early recognition of illness and intervention in BD. Increased feelings of anger in unipolar patients in combination with some other known clinical characteristics such as multiple brief depressed episodes, a lack of response to antidepressants, a family history of BD[58] might help to signal an upcoming conversion to BD. In addition, agitated affective states in BD patients deserve attention for its own sake, as these may have negative consequences for their quality of life and that of their loved ones[59]. Since BD patients experience extensive emotional instability even during euthymic states[15] and seem to use maladaptive strategies[60], it is important that they learn to regulate such feelings in an appropriate way. Psychotherapy, social therapy, and group-oriented approaches can help BD patients to prevent decompensation and to develop healthier social relationships. Other treatment strategies that may especially be apt to improve emotion regulation are dialectical behaviour therapy (DBT) and Systems Training for Emotional Predictability and Problem Solving (STEPPS) program, which is based on cognitive behavioural therapy combined with emotional management skill training[61, 62].

One of the strengths of this study is its longitudinal design and the inclusion of a large group of participants that oversampled patients with (preceding) depression. This is the first study that investigated prospectively the predictive value of feelings of anger in conversion to BD. In addition, this is the first study that examined five different constructs of anger in relation to BD, with strong and consistent findings. There are also limitations that need to be addressed. First, the primary focus of this prospective cohort study on unipolar rather than bipolar depression resulted in a relatively small sample of patients who experienced a (hypo)manic episode during follow-up. Second, even though we adjusted for potential confounders, a family history of BD was not assessed and could not be included as cofounder. Third, the current use of antipsychotic medication and mood stabilizers might have had a dampening effect on anger and aggression, leading to an underestimation rather than an overestimation of our results. However, the group taking these medications was fairly small. Lastly, participants who dropped out or missed scales at follow-ups had probably higher risk of anger or irritability. Exclusion of this specific group might have led to underestimation of our results.

We can conclude that aggression reactivity is a robust risk factor for the conversion from unipolar to bipolar disorder. In addition, patients who had experienced (hypo)mania (and thus had converted to BD) showed more feelings of anger in comparison with unipolar depressive patients. Identifying the potential risk factors for the development of BD might have clinical value in earlier recognition, prevention of conversion into mania, and better targeted interventions.

Bibliography

1. Judd LL et al. “The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders?” In: *J. Affect. Disord.* 73.1-2 (2003), pp. 19–32.
2. Perlis RH et al. *Revisiting Depressive-Prone Bipolar Disorder: Polarity of Initial Mood Episode and Disease Course Among Bipolar I Systematic Treatment Enhancement Program for Bipolar Disorder Participants.* 2005.
3. Gilman SE, Dupuy JM, and Perlis RH. “Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on Alcohol and Related Conditions”. In: *J. Clin. Psychiatry* 73.6 (2012), pp. 829–836.
4. Bowden CL. “A different depression: clinical distinctions between bipolar and unipolar depression”. In: *J. Affect. Disord.* 84.2-3 (2005), pp. 117–125.
5. Dom G and Moggi F, eds. *Co-occurring Addictive and Psychiatric Disorders: A Practice-Based Handbook from a European Perspective.* Vol. 8. Berlin, Heidelberg: Springer Berlin Heidelberg, 2015, pp. 163–163.
6. Perlis RH, Brown E, Baker RW, and Nierenberg AA. “Clinical features of bipolar depression versus major depressive disorder in large multicenter trials”. In: *Am. J. Psychiatry* 163.2 (2006), pp. 225–231.
7. Benazzi F and Akiskal H. “Irritable-hostile depression: further validation as a bipolar depressive mixed state”. In: *J. Affect. Disord.* 84.2-3 (2005), pp. 197–207.
8. Benazzi F. “Possible bipolar nature of irritability in major depressive disorder”. In: *J. Clin. Psychiatry* 66.8 (2005), 1072, author reply 1073.
9. Deffenbacher JL et al. “State-Trait Anger Theory and the utility of the Trait Anger Scale.” In: 43 (), pp. 131–148. ISSN: 1939-2168.
10. Spielberger CD, Reheiser EC, and Sydeman SJ. “Measuring the experience, expression, and control of anger”. In: *Issues Compr. Pediatr. Nurs.* 18.3 (1995), pp. 207–232.

11. Williams R. “Anger as a Basic Emotion and Its Role in Personality Building and Pathological Growth: The Neuroscientific, Developmental and Clinical Perspectives”. In: *Front. Psychol.* 8 (2017), p. 1950.

12. Spielberger C. “Manual for the State-Trait A02nger-expression Inventory. Odessa”. In: *Psychological Assessment Resources* (1991).

13. Fava M, Anderson K, and Rosenbaum JF. “"Anger attacks": possible variants of panic and major depressive disorders”. In: *American Journal of Psychiatry* 147.7 (7 1990), pp. 867–870. ISSN: 0002-953X.

14. Fava M et al. “Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment”. In: *Am. J. Psychiatry* 150.8 (1993), pp. 1158–1163.

15. Henry C et al. “Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period”. In: *Psychiatry Res.* 159.1-2 (2008), pp. 1–6.

16. Abrams R and Taylor MA. “A comparison of unipolar and bipolar depressive illness”. In: *Am. J. Psychiatry* 137.9 (1980), pp. 1084–1087.

17. Mammen OK, Pilkonis PA, Chengappa KNR, and Kupfer DJ. “Anger attacks in bipolar depression: predictors and response to citalopram added to mood stabilizers. Predictors and Response to Citalopram Added to Mood Stabilizers”. In: *J. Clin. Psychiatry* 65.5 (2004), pp. 627–633. ISSN: 0160-6689.

18. Benazzi F and Akiskal HS. “Psychometric delineation of the most discriminant symptoms of depressive mixed states”. In: *Psychiatry Res.* 141.1 (2006), pp. 81–88.

19. Ballester J et al. “Is bipolar disorder specifically associated with aggression?” In: *Bipolar Disord.* 14.3 (2012), pp. 283–290.

20. Perlis RH et al. “The prevalence and clinical correlates of anger attacks during depressive episodes in bipolar disorder”. In: *J. Affect. Disord.* 79.1-3 (2004), pp. 291–295.

21. Ballester J et al. “Prospective longitudinal course of aggression among adults with bipolar disorder”. In: *Bipolar Disord.* 16.3 (2014), pp. 262–269.

22. Aas M et al. “Affective lability in patients with bipolar disorders is associated with high levels of childhood trauma”. In: *Psychiatry Res.* 218.1-2 (2014), pp. 252–255.

23. Aas M et al. “Psychometric properties of the Affective Lability Scale (54 and 18-item version) in patients with bipolar disorder, first-degree relatives, and healthy controls”. In: *J. Affect. Disord.* 172 (2015), pp. 375–380.

24. Dutra SJ, Reeves EJ, Mauss IB, and Gruber J. “Boiling at a different degree: an investigation of trait and state anger in remitted bipolar I disorder”. In: *J. Affect. Disord.* 168 (2014), pp. 37–43.

25. Johnson SL and Carver CS. “Emotion-relevant impulsivity predicts sustained anger and aggression after remission in bipolar I disorder”. In: *J. Affect. Disord.* 189 (2016), pp. 169–175.

26. Edge MD et al. “People with bipolar I disorder report avoiding rewarding activities and dampening positive emotion”. In: *J. Affect. Disord.* 146.3 (2013), pp. 407–413.

27. Gruber J, Kogan A, Mennin D, and Murray G. “Real-world emotion? An experience-sampling approach to emotion experience and regulation in bipolar I disorder”. In: *J. Abnorm. Psychol.* 122.4 (2013), pp. 971–983.

28. Havermans R, Nicolson NA, Berkhof J, and deVries MW. “Mood reactivity to daily events in patients with remitted bipolar disorder”. In: *Psychiatry Res.* 179.1 (2010), pp. 47–52.

29. Knowles R et al. “Stability of self-esteem in bipolar disorder: comparisons among remitted bipolar patients, remitted unipolar patients and healthy controls 1”. In: *Bipolar Disord.* 9.5 (2007), pp. 490–495.

30. Kolla NJ, Meyer JH, Bagby RM, and Brijmohan A. “Trait Anger, Physical Aggression, and Violent Offending in Antisocial and Borderline Personality Disorders”. In: *J. Forensic Sci.* 62.1 (2017), pp. 137–141.

31. Bauer M and Pfennig A. “Epidemiology of bipolar disorders”. In: *Epilepsia* 46 Suppl 4 (2005), pp. 8–13.

32. Deltito J et al. “Do patients with borderline personality disorder belong to the bipolar spectrum?” In: *J. Affect. Disord.* 67.1-3 (2001), pp. 221–228.

33. Barzman DH, DelBello MP, Fleck DE, Lehmkuhl H, and Strakowski SM. “Rates, types, and psychosocial correlates of legal charges in adolescents with newly diagnosed bipolar disorder”. In: *Bipolar Disord.* 9.4 (2007), pp. 339–344.

34. Renaud S, Corbalan F, and Beaulieu S. “Differential diagnosis of bipolar affective disorder type II and borderline personality disorder: analysis of the affective dimension”. In: *Compr. Psychiatry* 53.7 (2012), pp. 952–961.

35. Penninx BWJH et al. “The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods”. In: *Int. J. Methods Psychiatr. Res.* 17.3 (2008), pp. 121–140.

36. Bles NJ de et al. “Trait anger and anger attacks in relation to depressive and anxiety disorders”. In: *J. Affect. Disord.* 259 (2019), pp. 259–265.

37. Van der Does W. “Thought suppression and cognitive vulnerability to depression”. In: *Br. J. Clin. Psychol.* 44.Pt 1 (2005), pp. 1–14.

38. Van der Does W. “Different types of experimentally induced sad mood?” In: *Behav. Ther.* 33.4 (2002), pp. 551–561.

39. Wittchen H.-U et al. “Cross-cultural Feasibility, Reliability and Sources of Variance of the Composite International Diagnostic Interview (CIDI)”. In: *British Journal of Psychiatry* 159.5 (1991), pp. 645–653.

40. Lecrubier Y et al. “The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI”. In: *European Psychiatry* 12.5 (1997), pp. 224–231.

41. Van der Ploeg HM, Defares PB, and Spielberger CD. “Handleiding bij de Zelf-analyse Vragenlijst”. In: *The Netherlands: Swets & Zeitlinger, Lisse* (1982).

42. Spielberger CD et al. “Preliminary manual for the state-trait anger scale (STAS)”. In: *Tampa: University of South Florida Human Resources Institute* (1980).

43. Spielberger CD, Krasner SS, and Solomon EP. “The Experience, Expression, and Control of Anger”. In: *Individual Differences, Stress, and Health Psychology.* Ed. by Janisse MP. New York, NY: Springer New York, 1988, pp. 89–108.

44. Hyler SE et al. “The Personality Diagnostic Questionnaire: Development and Preliminary Results”. In: *J. Pers. Disord.* 2.3 (1988), pp. 229–237.

45. Stringer B et al. “Recurrent suicide attempts in patients with depressive and anxiety disorders: the role of borderline personality traits”. In: *J. Affect. Disord.* 151.1 (2013), pp. 23–30.

46. Furnham A, Milner R, Akhtar R, and De Fruyt F. “A review of the measures designed to assess DSM-5 personality disorders”. In: *Psychology* 5.14 (2014), p. 1646.

47. Rush AJ, Gullion CM, Basco MR, Jarrett RB, and Trivedi MH. “The Inventory of Depressive Symptomatology (IDS): psychometric properties”. In: *Psychological Medicine* 26.3 (1996), pp. 477–486.

48. Beck AT, Epstein N, Brown G, and Steer RA. “An inventory for measuring clinical anxiety: Psychometric properties.” In: *Journal of Consulting and Clinical Psychology* 56.6 (1988), pp. 893–897.

49. Garno JL, Gunawardane N, and Goldberg JF. “Predictors of trait aggression in bipolar disorder”. In: *Bipolar Disord.* 10.2 (2008), pp. 285–292.

50. Becerra R et al. “Emotion regulation and residual depression predict psychosocial functioning in bipolar disorder: Preliminary study”. In: *Universitas Psychologica* 14.3 (2015), pp. 855–864.

51. Rive MM et al. “State-Dependent Differences in Emotion Regulation Between Unmedicated Bipolar Disorder and Major Depressive Disorder”. In: *JAMA Psychiatry* 72.7 (2015), pp. 687–696.

52. Vázquez GH et al. “Mixed symptoms in major depressive and bipolar disorders: A systematic review”. In: *J. Affect. Disord.* 225 (2018), pp. 756–760.

53. Fletcher K, Parker G, and Manicavasagar V. “Behavioral Activation System (BAS) differences in bipolar I and II disorder”. In: *J. Affect. Disord.* 151.1 (2013), pp. 121–128.

54. Fuhr K, Hautzinger M, and Meyer TD. “Implicit motives and cognitive variables: specific links to vulnerability for unipolar or bipolar disorder”. In: *Psychiatry Res.* 215.1 (2014), pp. 61–68.

55. Kelly RE et al. “Extreme positive and negative appraisals of activated states interact to discriminate bipolar disorder from unipolar depression and non-clinical controls”. In: *J. Affect. Disord.* 134.1-3 (2011), pp. 438–443.

56. Mansell W et al. “Extreme Appraisals of Internal States in Bipolar I Disorder: A Multiple Control Group Study”. In: *Cognit. Ther. Res.* 35.1 (2011), pp. 87–97.

57. Tosun A, Maçkali Z, Çağin Tosun Ö, Kapucu Eryar A, and Mansell W. “Extreme Appraisals of Internal States and Duration of Remission in Remitted Bipolar Patients”. In: *Noro Psikiyatr Ars* 52.4 (2015), pp. 406–411.

58. Ghaemi SN, Boiman EE, and Goodwin FK. “Diagnosing Bipolar Disorder and the Effect of Antidepressants. A Naturalistic Study”. In: 61 (2000), pp. 804–808. ISSN: 0160-6689.

59. Lee Mortensen G, Vinberg M, Lee Mortensen S, Balslev Jørgensen M, and Eberhard J. “Bipolar patients’ quality of life in mixed states: a preliminary qualitative study”. In: *Psychopathology* 48.3 (2015), pp. 192–201.

60. Zhang L et al. “Distinct temporal brain dynamics in bipolar disorder and schizophrenia during emotion regulation”. In: *Psychol. Med.* 50.3 (2020), pp. 413–421.

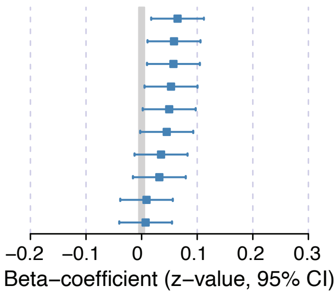
61. Eisner L et al. “Dialectical Behavior Therapy Group Skills Training for Bipolar Disorder”. In: *Behav. Ther.* 48.4 (2017), pp. 557–566.

62. Van Dijk S, Jeffrey J, and Katz MR. “A randomized, controlled, pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder”. In: *J. Affect. Disord.* 145.3 (2013), pp. 386–393.

3.6 Supplementary Figures & Tables

Trait Anger

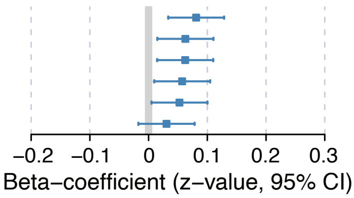
Item	Beta (95% CI)	P–value
7. Saying nasty things	0.065 (0.017; 0.112)	0.008
1. Quick tempered	0.058 (0.011; 0.106)	0.017
5. Hot–tempered	0.057 (0.010; 0.105)	0.018
2. Fiery temper	0.053 (0.005; 0.100)	0.030
3. Hotheaded person	0.050 (0.002; 0.097)	0.041
9. Easily irritated	0.045 (−0.003; 0.093)	0.064
4. Offended easily	0.035 (−0.013; 0.083)	0.151
6. Loose self–control	0.032 (−0.016; 0.079)	0.188
8. Furious when criticized	0.009 (−0.038; 0.056)	0.714
10. Infuriated after poor evaluation	0.007 (−0.040; 0.055)	0.765



Supplementary Figure 1: Associations of individual items of trait anger estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.

Aggression reactivity

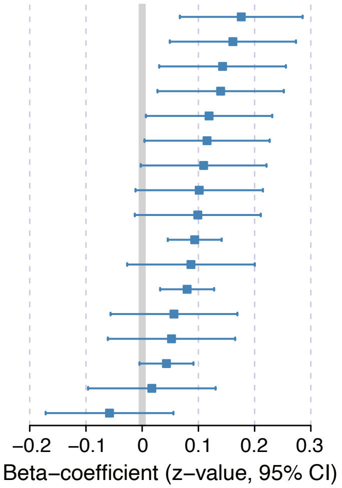
Item	Beta (95% CI)	P–value
26. Take more risk	0.081 (0.033; 0.129)	0.001
18. Feel like breaking things	0.063 (0.015; 0.110)	0.010
22. Feel cynical/sarcastic	0.062 (0.015; 0.110)	0.011
21. Aggressive thoughts	0.057 (0.010; 0.105)	0.019
7. Impulsiveness	0.053 (0.005; 0.100)	0.030
29. Lose temper easily	0.031 (−0.017; 0.078)	0.211



Supplementary Figure 2: Associations of individual items of aggression reactivity estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.

Anger Attacks

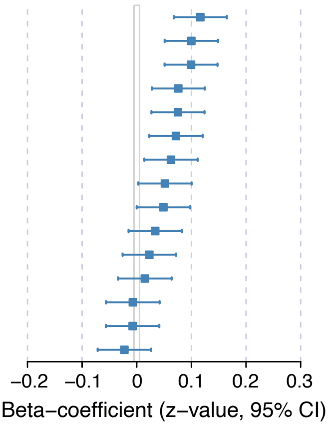
Item	Beta (95% CI)	P–value
10. Shortness of breath	0.176 (0.067; 0.285)	0.002
6. Hot flashes	0.161 (0.049; 0.274)	0.005
8. Paresthesia	0.143 (0.030; 0.256)	0.013
12. Trembling	0.140 (0.027; 0.252)	0.015
9. Dizziness	0.119 (0.007; 0.231)	0.039
7. Chest Tightness	0.115 (0.004; 0.227)	0.043
11. Sweating	0.109 (–0.002; 0.221)	0.056
16. Attacking pysically/verbally	0.101 (–0.012; 0.215)	0.080
14. Feeling out of control	0.099 (–0.013; 0.211)	0.084
3. Anger attacks	0.093 (0.046; 0.141)	0.000
15. Feeling like attacking others	0.087 (–0.027; 0.200)	0.135
1. Easily angry	0.080 (0.032; 0.128)	0.001
17. Throwing/destroying objects	0.057 (–0.056; 0.169)	0.327
5. Tachycardia	0.052 (–0.061; 0.165)	0.367
2. Overreact	0.043 (–0.005; 0.091)	0.078
13. Panic	0.017 (–0.096; 0.131)	0.767
4. Number of anger attacks	–0.058 (–0.172; 0.056)	0.317



Supplementary Figure 3: Associations of individual items of anger attack estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.

Borderline personality traits

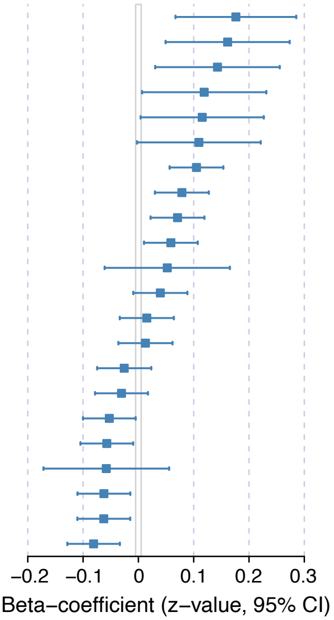
Item	Beta (95% CI)	P–value
69. Dull and meaningless life	0.116 (0.068; 0.165)	0.000
6. Separation anxiety.	0.100 (0.051; 0.149)	0.000
32. Self–identification	0.099 (0.051; 0.148)	0.000
19. Either love or hate	0.076 (0.028; 0.124)	0.002
47. Physical fights	0.075 (0.027; 0.124)	0.002
58. Moody	0.072 (0.023; 0.121)	0.004
98A. Spend too much	0.063 (0.014; 0.111)	0.012
93. Paranoid or black out	0.052 (0.003; 0.100)	0.038
98D. Taking drugs	0.049 (0.000; 0.098)	0.050
45. Self–harm	0.034 (–0.015; 0.083)	0.174
98B. Sex with poeple I hardly know	0.023 (–0.026; 0.072)	0.356
98E. Eating binges	0.015 (–0.034; 0.064)	0.552
98C. Drinking too much	–0.007 (–0.056; 0.042)	0.776
78. Difficulty controlling anger	–0.008 (–0.056; 0.041)	0.763
98F. Reckless driving	–0.023 (–0.072; 0.026)	0.366



Supplementary Figure 4: Associations of individual items of borderline personality traits estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.

Antisocial personality traits

Item	Beta (95% CI)	P–value
99N. *Skipping school	0.176 (0.067; 0.285)	0.002
99J. *Stole things	0.161 (0.049; 0.274)	0.005
99L. *Destroyed property	0.143 (0.030; 0.256)	0.013
99M. *Ran away from home	0.119 (0.007; 0.231)	0.039
99K. *Set fires	0.115 (0.004; 0.227)	0.043
99O. *Broke in	0.109 (–0.002; 0.221)	0.056
75. Enjoy risky things	0.105 (0.056; 0.154)	0.000
8. Trouble with law	0.079 (0.030; 0.127)	0.002
20. Physical fights	0.071 (0.022; 0.119)	0.004
94. Insensitive to harm others	0.059 (0.010; 0.107)	0.018
99I. *Stayed out at night	0.052 (–0.061; 0.165)	0.367
33. Financial instability	0.040 (–0.009; 0.089)	0.112
59. Lying	0.015 (–0.034; 0.064)	0.542
46. Impulsive	0.013 (–0.036; 0.062)	0.609
99A. *Bullied others	–0.026 (–0.075; 0.023)	0.304
99G. Sexually abused others	–0.031 (–0.078; 0.017)	0.211
99B. *Started fights	–0.053 (–0.100; –0.005)	0.030
99D. *Robbed or mugged	–0.057 (–0.105; –0.010)	0.019
99H. *Lied	–0.058 (–0.172; 0.056)	0.317
99E. *Physically cruel to people	–0.062 (–0.110; –0.015)	0.011
99C. *Used a weapon in fights	–0.063 (–0.110; –0.015)	0.010
99F. *Physically cruel to animals	–0.081 (–0.129; –0.033)	0.001



Supplementary Figure 5: Associations of individual items of antisocial personality traits estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.
∗Childhood antisocial personality traits.

CHAPTER 4

Effects of the COVID-19 pandemic in a preexisting longitudinal study of patients with recently diagnosed bipolar disorder: indications for increases in manic symptoms

Koenders, M.*, Mesbah, R.*, Spijker, A., Boere, E., de Leeuw, M., van Hemert, B., & Giltay, E. (2021). Effects of the COVID-19 pandemic in a preexisting longitudinal study of patients with recently diagnosed bipolar disorder: Indications for increases in manic symptoms. *Brain and Behavior*, 11(11), e2326. DOI: 10.1002/brb3.2326

∗ Shared co-first authorship

Abstract

Background
The coronavirus disease 2019 (COVID-19) pandemic interfered in the daily lives of people and is assumed to adversely affect mental health. However, the effects on mood (in)stability of bipolar disorder (BD) patients and the comparison to pre-COVID-19 symptom severity levels are unknown.

Method
Between April and September, 2020, symptoms and well-being were assessed in the Bipolar Netherlands Cohort (BINCO) study of recently diagnosed patients with BD I and II. The questionnaire contained questions regarding manic and depressive symptoms (YMRS and ASRM, QIDS), worry (PSWQ), stress (PSS), loneliness, sleep, fear for COVID-19, positive coping, substance use. As manic, depressive and stress symptoms levels were assessed pre-COVID-19, their trajectories during the lockdown restrictions was estimated using mixed models.

Results
Of the 70 invited BD patients 36 (51%) responded at least once (mean age of 36.7 years, 54% female, and 31% BD type 1) to the Covid-19 assessments. There was a significant increase (X^2 = 17.06; p = 0.004) in (hypo)manic symptoms from baseline during the first COVID-19 wave, with a decrease thereafter. Fear of COVID-19 (X^2 = 18.01; p =0.003) and positive coping (X^2 = 12.44; p = 0.03) were the highest at the start of the pandemic and decreased thereafter. Other scales including depression and stress symptoms did not vary significantly over time.

Conclusion
We found a meaningful increase in manic symptomatology from pre-COVID-19 into the initial phases of the pandemic in BD patients. These symptoms decreased along with fear of COVID-19 and positive coping during the following months when lockdown measures were eased.

4.1 Introduction

By the beginning of 2020, the coronavirus disease 2019 (COVID-19) outbreak started to spread around the world. In order to contain the virus, drastic measures were needed that interfered in the daily lives of people. The threat of the disease itself and the disruptive daily-life consequences of lockdown measures appear to have significant impact on mental well-being. Previous research on the effects of quarantines (non-COVID-19 related) showed significant negative psychological impact on the general population (e.g. post-traumatic stress, frustration, anger, fear and boredom)[1]. Preliminary studies on the effects of COVID-19 lockdowns reported adverse changes in sleep patterns and decreased quality of sleep[2]. Internet-searches on topics such as boredom, loneliness, worry and sadness increased drastically, suggesting that mental health is affected by the measures[3]. Additionally, in an online survey among 1,210 healthy respondents, 55% experienced a moderate to severe psychological impact, and 17% and 29% reported depressive and anxiety symptoms, respectively. Most respondents were worried about family members becoming infected (75%) and spent 20-24 h per day at home (85%). Women and those with physical symptoms and poorer health had higher anxiety and depression[4].

Because of these reported negative effects on the general population, several concerns have been raised regarding its effects on patients with psychiatric disorders[5]. There are indications that people with higher symptom levels of depression, anxiety and stress symptomatology suffer most from the lockdown measures[2]. People suffering from psychiatric disorder were found to be more severely impacted by the pandemic than healthy controls and reported (cross-sectionally) more severe increases of stress-related symptomatology like depressed mood, anxiety, and sleep problems[6].

Among people suffering from psychiatric disorders, a specifically vulnerable group to the effects of the COVID-19 measures might be patients suffering from bipolar disorder (BD), a specifically vulnerable group to the effects of the COVID-19 measures might be patients suffering from bipolar disorder (BD), especially because major life events are consistently identified as triggers for mood instability in BD[7]. Obviously a pandemic is not comparable to major life events such as the loss of a close relative, getting married or moving house. Natural disasters might be comparable to only some extent, in which the current pandemic disrupts daily lives of almost all citizens. Although the influence of a pandemic on patients with BD is unknown, a previous study on the effect of the Fukushima disaster already showed that a major life event could specifically exacerbate symptoms of BD, especially manic symptoms (and did not lead to increase in symptomatology in other psychiatric disorders)[8]. In case of the COVID-19 pandemic, the lockdown measures seemed to interfere specifically with factors that are essential for bipolar mood stability, affecting social rhythm and sleep. This may induce a relapse into both depression and (hypo)mania (see reviews by[9, 10]. A study into the effect of a natural disaster (earthquake) on bipolar and schizophrenic patients, showed that both groups reported less social support and more avoidance[11]. Recent cross-sectional studies have shown that COVID-19 pandemic was associated with a higher frequency of depressive episodes and alterations in biological rhythm in patients with BD[12, 13, 14]. These studies found associations lockdown measures and depression severity and alterations in biological rhythm including impaired sleep, activity and social rhythm[12], with a potential increased effect on BD patients compared to unipolar patients and healthy controls[14]. The later study was extended with verified

BD diagnoses (N=43) and the findings revealed relatively mild (mostly non-significant) pandemic-related depressive mood symptoms, which was ascribed to some development of resilience[13]. Finally, in an observational prospective study on affective disorders that included BD (N = 194) a low impact of Covid-19 on mental health was found[15], similar to our findings. In order, to effectively weigh the impact of the COVID-19 outbreak, comparison of pre-COVID-19 and post-COVID-19 severity levels is needed. Only few studies to date have been able to study the mental health impact of the COVID-19 using such a design. One of those studies showed that patients with and without depressive, anxiety, or obsessive-compulsive disorders experienced an adverse impact on their mental health from the COVID-19 pandemic. Yet, those with the highest burden of mental illness tended to show no increase or even a slight symptom decrease[16]. We are aware of only two studies of the impact of COVID-19 in patients with BD, that compared prepandemic symptom levels to post-pandemic levels. In the study by Orhan et al. (2020)[17] among older (over age 50) patients with BD comparable results with the study we previously mentioned were found: no worsening of symptom levels were observed among these patients. Actually symptom levels significantly decreased among these patients. They did find that passive coping and loneliness were associated with symptom increase. The results of a 1 month prospective study[18] showed that BD patients were more affected by the lockdown restrictions with regard to life impact changes in biological and social rhythm, income and employment and pandemic stress compared to healthy controls. Interestingly, the healthy control group showed an increase in depressive symptom severity during the pandemic when compared to pre pandemic scores, whereas BD patients did not show a significant change in symptom severity.

The current study longitudinally investigates the effect of COVID-19 measures in the Netherlands in an existing cohort of recently diagnosed and relatively young adults with BD, who were followed from the first months of the Dutch lockdown restrictions, into the period in which measures were temporarily eased. Of all participants pre-pandemic data on symptom levels and perceived stress is available. The aim of the study is to investigate the mental health impact of the pandemic in bipolar disorder patients in terms of symptoms levels, loneliness, worry, stress and specific COVID-19 related factors (e.g., fear of COVID-19, coping). We additionally investigate whether specific factors are related to an increase in manic and depressed symptomatology.

4.2 Materials and Methods

4.2.1 Participants

Patients from the Bipolar Netherlands Cohort (BINCO) study were enrolled in the current study. This is a Dutch cohort in which recently diagnosed ($<$ 1 year) bipolar I and II patients are included from different mental health outpatients clinics in the Netherlands. Clinical data such as mood status and received treatment are collected every half year; cognitive function, lifestyle factors, psychological characteristics, genetic, neuro-imaging, endocrine and immune status are assessed at baseline and after 1 year. Of the 70 patients that were enrolled in the study, 36 were willing to participate in the current substudy.

The group included (n=36) is compared with the group of subjects who did not participate (n=34) in this substudy. There were no significant differences in age, gender, type of BD, mania (YMRS) and depression (QIDS) total scores between these two groups at baseline.

4.2.2 Procedure

This is an ecological add-on study to BINCO which was approved by the medical ethical committee of the Leiden University Medical Centre. We aimed to observe the incidence of mood change during the current COVID-19 epidemic in the Netherlands. After verbal agreement to participate in the study, participants received the first online questionnaire. Because no face to face contacts were allowed during this period, participants signed informed consent in the online questionnaire. Subsequently, they received a repeated online questionnaire every month, with an additional telephone interview. In total, there were 6 repeated measurements (timepoint 1 [T1] to timepoint 6 [T6]), starting from April 2020 when the first lockdown in the Netherlands started, into October when the second corona wave started. During the summer (July and August) there was a break and there were no measurements. Supplemental Figure 4.2 gives an overview of the timing of the measurements in relation to the COVID-19 pandemic in the Netherlands, and its related lockdown measures. During the initial months of the pandemic, the most strict measures came into effect by the midst of March 2020, when schools, universities, day-care, bars, restaurants and other public places were closed. Most working people were only allowed to work from home, and clear restrictions were set on social gatherings inside and outside people's homes. Also, mental health care was mainly delivered through telephone- or video consultations. The Dutch measures were slightly less strict compared to other European countries, since people have been advised to stay at home, but were still allowed to go outside as long as 1.5 meter (5ft) social distance was maintained. Nevertheless, the measures had a significant impact on daily lives of people.

The response rate was good for the majority of the follow-up measurements, with a relatively low response on T5: T1: 92% (N=33), T2: 83% (N=30), T3: 83% (N=30), T4: 67% (N=24), T5: 33% (N=12), T6: 78% (N=28).

4.2.3 Materials

The Composite International Diagnostic Interview (CIDI) 2.1 Lifetime Dutch version (Section E, depression, Section F, mania) was used to confirm bipolar diagnosis in the BINCO sample at pre-COVID-19 baseline. The assessment of the CIDI was not part of the current COVID-19 procedure.

The following measurements were repeatedly assessed in this substudy.

Corona specific questionnaires

To assess Corona-related information we composed a brief questionnaire containing 4 subgroups of items: fear of COVID-19 (six items; Cronbach's $\alpha= \cdot 81$), positive coping (six items; $\alpha= \cdot 79$), sleep disturbance (three items, $\alpha= \cdot 60$) and alcohol use and smoking (two items, $\alpha= \cdot 70$). This questionnaire was adapted from another recent study into the effects of COVID-19 on psychiatric patients[16]. Answer categories were on a 5-point Likert scale: 1 (completely disagree) to 5 (completely agree). A complete listing of the items is given in supplementary Table 4.2.

Questionnaires on psychological well-being

Depressed symptoms
The 16 items Quick Inventory of Depressive Symptomatology (QIDS-SR)[19] was used to repeatedly assess symptoms of depression in the past two weeks. The QIDS-RS questionnaire was previously completed at baseline (prepandemic) and during the 6 follow-up measurement during the pandemic. The questionnaire covers the 9 DSM 5 criteria of depression and has good internal consistency, also for the Dutch translation (Cronbach's alpha $> .86$)[20]. Cronbach's alpha in the current study was 0.82.

Manic symptoms
In order to assess (hypo)manic symptoms both the clinician-rated, 11-item Young Mania Rating Scale (YMRS)[21] and the 5-item self-report Altman Self-Rating Mania Scale (ASRM)[22] were used.

The YMRS was assessed at baseline (prepandemic) and 5 times during the follow-up measurement by brief telephone interviews. The items are scored based on the patient report and the clinical impression by the interviewer. The YMRS has good inter-rater reliability (r=.93)[21] which has been confirmed for the Dutch translation[23]. Internal consistency (Cronbach's alpha) in the current sample was .85.

The ASRM is a five item self-report measure of current (hypo)manic symptoms[22]. Total scores of ≥ 6 indicates a high probability of a manic or hypomanic state. The questionnaire has good internal consistency (Cronbach's alpha=.79). It has the ability to detect hypomania or mania with a sensitivity of .85 and a sensitivity of .87[22]. The Dutch version has not yet been validated.

Loneliness (DeJong Q)

For the assessment of loneliness the 6-item Jong Loneliness Scale-short version (DeJong Q) was used. This questionnaire assesses social (e.g. number of relationships) and emotional loneliness (e.g. aspired relationships) on a 3-point scale (no, more or less, yes), resulting in a minimum score of 0 and a maximum score of 12. The short version has good test-retest reliability, ranging between r=.81 to r=.95 in different samples[24]. Internal consistency of the scale in the current sample was .72.

Worry (PSWQ)

To assess changes in the reported amount of trait worry the Penn State Worry questionnaire (PSWQ)[25] abbreviated 11-item version was used[26]. The Dutch translation has good internal consistency in clinical samples ($>$ 0.83) (Cronbach's alpha)[27, 28]. The questionnaire assesses pathological worry and its characteristics on a 5-point Likert scale. Internal consistency of the Worry questionnaire in the current sample was .91 (Cronbach's alpha).

Perceived stress (PSS)

The perceived Stress Scale 10-item short version[29], was used to measure changes in the amount of stress patients subjectively experienced in the past two weeks. This questionnaire was completed at baseline (prepandemic) and during the 6 follow-up measurement during the pandemic. The questionnaire measures the extent to which respondents consider their lives to be unpredictable, uncontrollable and overloaded (e.g. in the last two weeks, how often have you felt nervous and 'stressed'/been able to control your irritations, etc.) on a 5-point Likert scale. The scale has good internal consistency (Cronbach's alpha = .82)[30]. In current sample the internal consistency of this questionnaire was 0.86 (Cronbach's alpha). The questionnaire has been validated in numerous languages, but the Dutch version has not yet been validated[31].

4.2.4 Statistical Analyses

Baseline characteristics and sociodemographic were summarized as means (with standard deviations [SD]) for continues variables and as numbers for proportions for categorical variables. We considered a p-value less than .05 statistically significant. We averaged assessments of the baseline and one year assessments for the YMRS, QIDS and PSS severity scores that took place in 2017 and 2019 to yield the pre-COVID-19 severity levels among the 36 participants.

We used exploratory factor analysis (EFA) with Principal Axis Factoring and oblique rotations (i.e., Oblimin) to examine dimensionality of COVID-19-specific questionnaire. Four dimensions were determined based on the screeplot, evaluation of Eigenvalues (>1 indicates a distinct dimension), factor loadings, and conceptual plausibility. The four dimensions in the COVID-19 specific items were labelled as fear of COVID-19, positive coping, sleep disturbance and alcohol use and smoking. See supplement Table 4.1 for a list of the items and the factor loadings. One item about intensively following the COVID-19 news was omitted because it had factor loading of 0.25 or less on all the four dimensions.

In order to assess the changes in symptoms of depression, (hypo)mania, worry, perceived stress and loneliness before and during the COVID-19 pandemic the marginal mean scores were estimated for each wave. At baseline, the sum scores of QIDS, YMRS and PSS were also available. In addition to these questionnaires; ARSM, PSWQ, DeJong Q and scores of the 4 symptom dimension scales were assessed during the COVID-19 pandemic. Mixed models were used to compare marginal mean scores before and during the pandemic on symptom scales. All models were adjusted for age, gender, and the level of education.

Additionally, using linear regression analysis, we investigated whether age, gender, type of bipolar disorder and the four dimension scales of COVID-19 questionnaire predicted the course of depression or (hypo)manic symptoms. For this analysis all predictor variables were standardized in order for easier comparison of effect sizes among the different predictors. We tested for the interaction term of time $*$ predictors , in order to explore whether some variables predicted for a stronger linear increase over time in mania (YMRS) or depressive symptomatology (QIDS, with time as a continuous variable). Finally, to compare the in- and out-strengths of each of the 10 scale scores, we applied dynamic time ward (DTW) analyses of the time-series of 20 BD patients with 4 or more assessments during their trajectories[32]. The DTW distance between each pair of scale score was calculated (i.e., 40 distances per individual, for each of the 20 patients). In order to assess the direction of the effect a asymmetric window type was used with the size of the time window of 1 (so only 1 assessment afterwards was taken into account). The descriptive analysis and EFA were done in SPSS version 22. We used packages in R (version 3.6.0) for linear regression, mixed models (package 'lme4', version 1.1-21, and 'emmeans', version 1.4.3.01), for DTW analyses ('dtw', version 1.21-3), and for figures ('forestplot', version 1.9).

4.3 Results

4.3.1 Sample characteristics

Basic demographic and clinical characteristics of the sample (N = 36) are summarized in Table 4.1. The included subjects had a mean age of 36.7 (SD = 12.6) years and 44% were male. Two third of the participants were diagnosed with bipolar disorder type II (68.6) and had no partner (60.6%). At baseline, QIDS score was 11.2 (SD = 6.4), indicating moderate depressive symptoms and YMRS was 3.3 (SD = 3.8) indicating a low average severity of mania symptoms.

4.3.2 Changes in (hypo)manic, depressed and stress-related symptomatology before and during the COVID-19 pandemic

Figure 4.1 depicts average marginal mean levels over time of the three symptom scores (i.e., QIDS, YMRS and PSS) before and during the pandemic. Results of the mixed models analyses showed significant changes ($X^2 = 17.06$; $p = 0.004$) in manic symptoms (YMRS) from baseline (prepandemic) into the COVID-19 pandemic period. Compared to pre-COVID-19 levels manic symptoms increased significantly during the first two time points (T2 and T3 between April and May), which coincides with the most strict lockdown measures in the Netherlands. Mania severity decreased significantly from T2 to T3 (end of May) and stayed stable from that time point onwards. Self-reported manic symptoms (ASRM) were only measured during the COVID-19 pandemic (no pre-pandemic data available). Self-reported (hypo)mania on the ASRM indicate an overall clinically significant (hypo)manic state (mean $>$ 6), from April until June. No significant changes over time were found.

The depression symptoms (QIDS) showed a reverses trend, with symptoms decreasing at the beginning of the pandemic compared to baseline (prepandemic) and increasing back to baseline level during the summer, when lockdown measures were eased down. However, depressive symptom changes do not vary significantly over time, and overall mean symptom levels remain relatively mild both before and during the pandemic. No significant change from baseline into the pandemic was found for reported perceived stress among the bipolar patients.

4.3.3 Changes in COVID-19 related symptoms, loneliness and worry during the pandemic

Results of the four dimension scales of COVID-19-specific questionnaires (see Figure 4.1) showed significant changes in fear of COVID-19 ($X^2 = 18.01$; p =0 .003) and positive coping ($X^2 = 12.44$; $p = 0.03$) during the pandemic. In the beginning of the lockdown in April the fear of COVID-19 was the highest and it decreased significantly during the crisis. Positive coping showed the same trend, it was highest in the beginning of the crisis and it significantly decreased during the pandemic.

Table 4.1: Baseline sociodemographic characteristics in 36 participants with bipolar disorder.

	No. (%) or median (P_{25}-P_{75}) or mean (SD) (N=36)
Sociodemographic characteristics:	
Male, sex	16 (44.4%)
Age; mean (SD)	36.7 (12.6)
Level of education:	
- Primary	2 (5.6%)
- Secondary	14 (38.9%)
- Higher	20 (55.6%)
Current smoker	12 (34.3%)
Alcohol use	
- none	13 (37.1)
- 1-4 units per month	15 (42.9)
- $\geq$ 4 units per week	2 (5.7)
- a history of alcohol use	4 (11.4)
Drugs abuse	5 (14.3)
Marital status	
- No partner	20 (60.6%)
- With partner (not married)	4 (12.1%)
- Married	6 (18.2%)
- Divorced	3 (9.1%)
Children (yes)	12 (37.5%)
Clinical characteristics:	
Bipolar disorder type 1	11 (30.6%)
Age of onset; mean (SD)	
Age of onset first (hypo-) mania	22.9 (7.2)
Age of onset first depression	20.4 (8.5)
Age of onset disease	18.9 (7.5)
Number of episodes:	
- No. of (hypo)manic episodes; median (P_{25}-P_{75})	4 (2, 13)
- No. of depressive episodes; median (P_{25}-P_{75})	7 (6, 14)
QIDS baseline; mean (SD)	11.2 (6.4)
YMRS baseline; mean (SD)	3.3 (3.8)
Medication use baseline:	
- Lithium	20 (57.1%)
- Anti-epileptics	4 (12.5%)
- Anti-psychotics	10 (28.6%)
- Benzodiazepines	5 (15.6%)
- Antidepressants	8 (25.0%)

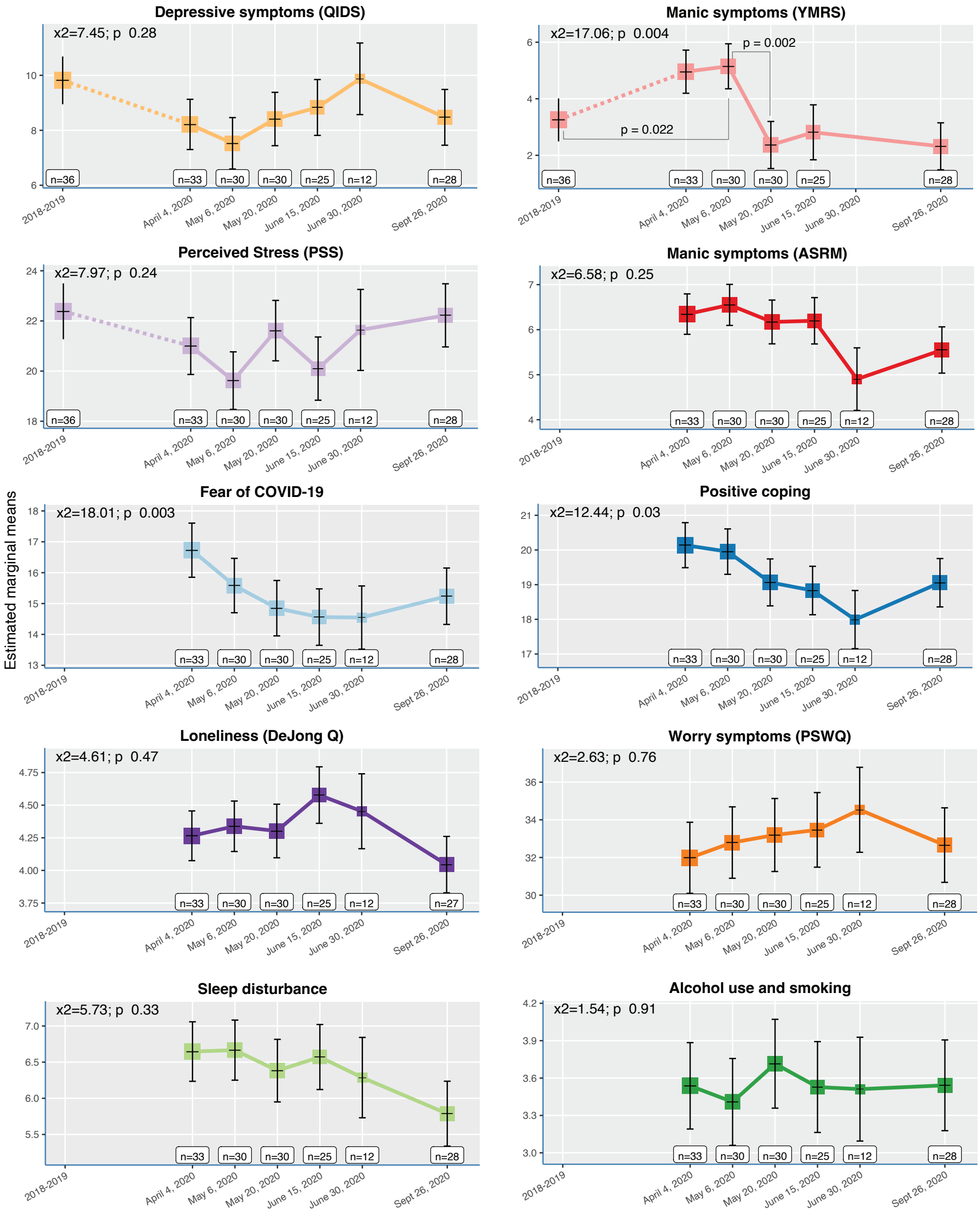


Figure 4.1: Trajectories of marginal mean symptom severity scores before and during the COVID-19 pandemic of symptoms of (hypo)mania (YMRS), depression (QIDS), and perceived stress (PSS). Trajectories of marginal mean scores of COVID-19 related symptoms (fear of COVID, positive coping, sleep disturbances, alcohol use and smoking), loneliness (DeJong Q), worry (PSQQ) and self-reported (hypo)mania on the ASRM during the pandemic. The number of included participants per wave are shown, and the size of each box is proportional to the number of subjects. Error bars represent standard errors. P-values by multilevel linear (mixed) models for the effects of time.

No significant mean changes over time were found for the COVID-19 specific scales of sleep disturbances, and alcohol use and smoking and for worry, and loneliness. Worry levels are were consistently high (mean $\geq$ 32) during the pandemic. We have repeated the analysis while removing T5 from the analyses, which resulted in similar significance levels for 9 out of the 10 outcomes. The trajectories for Fear of Covid-19 and Manic symptoms were still statistically significant (P=0.003 and P=0.004, respectively), whereas the trajectory of Positive Coping was no longer statistically significant (P=0.11 instead of P=0.03).

4.3.4 Predictors of mood symptoms

We then explored whether any of seven factors (i.e., age, sex, BD type II vs. I, fear of COVID-19, positive coping, sleep disturbance, and alcohol use and smoking) could predict for differential trajectories over time in (hypo)manic (YMRS) and depressive symptomatology (QIDS). Therefore, these potential interaction with time of these predictive factors were analyzed. Findings showed that none of these seven factor had significant predictive value for the course of (hypo)manic and depressive symptoms over time (see Supplementary Figure 4.3). Finally, we explored which change in symptom scale score preceded other changes in symptom scale score in 20 participants with 4 or more COVID-19 assessments (see supplementary Figure 4.4). We found that (hypo)manic and worry symptoms had the strongest out-strengths, which persisted when we divided the BD group into two random subgroups of 10. This indicates that increases and decreases in (hypo)manic and worry symptoms tended to be followed by increases and decreases of other scales, rather than vice versa.

4.4 Discussion

The current prospective study is among the first to investigate the impact of the COVID-19 pandemic and its lockdown measures on recently diagnosed BD patients in an existing cohort. In the current study we compared mania, depression, anxiety, and stress-related symptom levels before the pandemic with levels during the pandemic using up to six follow-up measurements in relatively young patients with bipolar disorder. We found that observer-rated (hypo)mania symptoms increased significantly during the first two months of the pandemic compared to the (hypo)mania levels before the pandemic. Further, during the pandemic, fear of COVID-19 and positive coping started of relatively high, but decreased significantly in the following months.

The initial increase of (hypo)manic symptoms during the pandemic compared to pre-pandemic mania levels was rather mild, based on the clinician-rated YMRS, although, the self-reported scores on the ASRM during the pandemic did suggest clinical significant (hypo)manic symptomatology. Combining these findings, it seems that there was a meaningful increase in (hypo)manic symptoms among bipolar disorders patients during the initial phase of the pandemic. One explanation for this increase could be the rather disruptive effect of the lockdown measures on the daily lives of the bipolar patients. Important cues for daily rhythms, such as going to work or study, bringing the kids to school, going to sport-clubs or other hobbies disappeared during the lockdown when everyone was expected to live and work from home as much as possible. BD patients might be particularly vulnerable to such disruptions in daily rhythms, which have been related to the onset of new mood episodes[33]. Three recent case reports support associations between COVID-19 pandemic and (hypo)manic symptoms. These case-studies all describe cases of individuals who developed a manic (psychotic) episodes during the COVID-19 pandemic, both in people with no prior history of any psychiatric condition[34] and in a patient that was already familiar with BD[35]. In all these cases the stress and daily rhythm disruptions of lockdowns and/or quarantine were presumed to be a trigger for the (first) onset of manic episodes. The fact that a previous study[17] among older patient with BD found a decrease in manic symptoms, while in our younger-aged cohort we found an increase might be explained by the fact younger people with BD are more vulnerable to life stressors than older adults. According to this inoculation-hypothesis older adults are better able to deal with life-stressors because they simply have more experience with this[36].

Lastly, besides the fact that it is likely that the disruptive lockdown measures caused affective instability in BD patients in the current study, this association might be spurious since the start of the lockdown and the rise of the (hypo)manic symptoms coincide with the spring season. Spring and the increase of daylight has been repeatedly associated with increases in (hypo)manic symptomatology[37] and therefore has to be mentioned as an alternative explanation.

Additionally, the disrupting effects for daily life of the pandemic, the accessibility of mental health care during the lockdown could also contribute to increased instability. Although, a recent study in the Netherlands showed that the availability of online treatment in many cases increased accessibility for patients, these methods also could lead to the missing of crucial information about a patient and rapid response to crises[38].

In the current study we observed a slight increase in depressive symptoms, although not significantly. Although cross-sectional studies have suggested that an increase in depressive symptoms was associated with the start of the pandemic[6], results from prospective, repeated measures, studies showed that participants with mental illness had higher levels of depressive and anxiety symptoms, but these symptoms decreased in the subsequent weeks of lockdown[16, 39]. For bipolar patients specifically, cross-sectional studies again indicated an increase in depressive symptomatology compared to comparison groups[12, 14], but prospective studies showed no substantial increases in depressive symptomatology compared to pre-pandemic measures[17, 18]. Possible explanations are that most patients have previously dealt with stressful events and social isolation caused by their mental illness and therefore have learned how to cope with stressful situations, and that the lockdown measured induced some sense of relaxation as their world and habits became more in sync with the quarantined society.

During the pandemic we found that fear of COVID-19 decreased significantly over time in BD patients. Presumably, with infection- and death rates decreasing, the fear of COVID-19 was also wearing off. A comparable trend in fear of Covid-19 during the course of the pandemic has been described in a previous study in the general population[40]. However, because we did not include a non-psychiatric comparison group, it is impossible to state that the initial fear of COVID-19 is related to having a BD.

Although fear was increased during the initial months in the current study, we also found that positive coping was high. During the first months the use of positive coping styles like staying active, feeling connected, being socially connected to other people, etc. started rather high, but decreased over the following months. This trend could be caused by patients trying to make the best of it at the beginning of the pandemic, but failed to keep this positivity when time progressed. Previous studies in the general population only found weak associations between positive coping styles and well-being[41, 42], which might lead to demotivation over time to maintain a positive attitude. Alternatively, the positive attitude in the current study seems to show a parallel course with the increase and decrease of (hypo)manic symptoms, so could also be related to the energetic, positive and often socially active (hypo)manic mood state. Either way, it seems that the current sample of patients with recent onset BD was able to use a positive coping style during the most strict lockdown measures, and this attitude decreases somewhat when lockdown measures were eased down. In addition, 55.6% of the participants were highly educated. Associations have been found between the level of education, emotional intelligence, resilient behaviors, and coping skills[43]. Coping in the face of the Covid-19 pandemic may have been moderated by the level of education, which should be studied in larger samples of BD patients.

The current study is among the first to repeatedly assess symptoms in the same BD patients both before and during the COVID-19 pandemic. The sample contains recently diagnosed bipolar patients of a relatively young age, in the active stages of their lives (with study, work, and family circumstances) in which the impact of the lockdown is highly invasive, and therefore this is an important at-risk group to study.

There are also some limitations to the current study. First, the sample size is rather small. Of the original 70 patients included in the BINCO study, only 36 participated in the current study. However, there were no differences between these in age, gender, education level, type of BD and severity of depression or (hypo)manic symptoms among participants and non-responders. Our findings were limited to relative small sample of recently diagnosed BD patients, and may have been underpowered to detect more subtle trends in mental health. We did not gather data on some other variables than may explain some of the changes found over time (eg, comorbid psychiatric disorders, vulnerability to seasonal variations, or non-adherent to medication). Additionally, the use of self-report measures might have let to response biases.

Another limitation is the lack of a healthy comparison group. As a consequence, we were not able to determine whether BD patients were more, less or equally affected by the pandemic compared to healthy controls. A previous study among depressed and anxious patients showed that worry and loneliness symptoms were increased in the non-psychiatric control group[16]. It is likely that our BD patients were already higher in symptomatology compared to non-psychiatric controls, and that these did not further increase during the pandemic. Moreover, although we had six repeated measurement points, no data was collected during summer break because of an anticipated lower response rates due to summer holidays of the participants.

4.5 Conclusion

The most important finding of the current study is that there is a meaningful increase in (hypo)manic symptomatology in recently diagnosed bipolar disorder patients, during the initial phases of the COVID-19 pandemic compared to pre-pandemic symptomatology. (Hypo)manic and worry symptomatology were the most influential with regard to all affective and COVID-19 related scales. Therefore, it could be hypothesized that to limit the psychological and psychiatric impact of a stressful crisis like the COVID-19 pandemic on BD patients, it would probably be effective to target worry and (hypo)manic symptoms in psychotherapeutic and pharmacological treatment sessions.

Since the increase in (hypo)manic symptomatology was rather mild, and no severe manic (psychotic) decompensations occurred in the current sample, these results could be interpreted as a sign of resilience and adaptability of this population, which has been proposed recently[44]. Nevertheless, the increase in symptoms still means that BD patients need to be closely monitored (despite lockdown measures) during this pandemic, and future national and international crises as has been outlined by clinicians in the field[45].

Bibliography

1. Brooks SK et al. “The psychological impact of quarantine and how to reduce it: rapid review of the evidence”. In: *Lancet* 395.10227 (2020), pp. 912–920.
2. Cellini N, Canale N, Mioni G, and Costa S. “Changes in sleep pattern, sense of time and digital media use during COVID-19 lockdown in Italy”. In: *J. Sleep Res.* 29.4 (2020), e13074.
3. Brodeur A, Clark AE, Fleche S, and Powdthavee N. “COVID-19, lockdowns and well-being: Evidence from Google Trends”. In: *J. Public Econ.* 193 (2021), p. 104346.
4. Wang C et al. *Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China*. 2020.
5. Yao H, Chen J.-H, and Xu Y.-F. “Patients with mental health disorders in the COVID-19 epidemic”. In: *Lancet Psychiatry* 7.4 (2020), e21.
6. Hao F et al. *Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry*. 2020.
7. Lex C, Bäzner E, and Meyer TD. “Does stress play a significant role in bipolar disorder? A meta-analysis”. In: *J. Affect. Disord.* 208 (2017), pp. 298–308.
8. Matsumoto J et al. “Mental disorders that exacerbated due to the Fukushima disaster, a complex radioactive contamination disaster”. In: *Psychiatry Clin. Neurosci.* 68.3 (2014), pp. 182–187.
9. Abreu T and Bragança M. “The bipolarity of light and dark: A review on Bipolar Disorder and circadian cycles”. In: *J. Affect. Disord.* 185 (2015), pp. 219–229.
10. Takaesu Y. “Circadian rhythm in bipolar disorder: A review of the literature”. In: *Psychiatry Clin. Neurosci.* 72.9 (2018), pp. 673–682.
11. Horan WP et al. “Stress and coping responses to a natural disaster in people with schizophrenia”. In: *Psychiatry Res.* 151.1-2 (2007), pp. 77–86.

12. Carta MG et al. “Living With Bipolar Disorder in the Time of Covid-19: Biorhythms During the Severe Lockdown in Cagliari, Italy, and the Moderate Lockdown in Tunis, Tunisia”. In: *Front. Psychiatry* 12 (2021), p. 634765.
13. Karantonis JA, Rossell SL, Berk M, and Van Rheenen TE. “The mental health and lifestyle impacts of COVID-19 on bipolar disorder”. In: *J. Affect. Disord.* 282 (2021), pp. 442–447.
14. Van Rheenen TE et al. “Mental health status of individuals with a mood-disorder during the COVID-19 pandemic in Australia: Initial results from the COLLATE project”. In: *J. Affect. Disord.* 275 (2020), pp. 69–77.
15. Tundo A, Betro’ S, and Necci R. “What Is the Impact of COVID-19 Pandemic on Patients with Pre-Existing Mood or Anxiety Disorder? An Observational Prospective Study”. In: *Medicina* 57.4 (2021).
16. Pan K.-Y et al. “The mental health impact of the COVID-19 pandemic on people with and without depressive, anxiety, or obsessive-compulsive disorders: a longitudinal study of three Dutch case-control cohorts”. In: *Lancet Psychiatry* 8.2 (2021), pp. 121–129.
17. Orhan M et al. “Psychiatric symptoms during the COVID-19 outbreak in older adults with bipolar disorder”. In: *Int. J. Geriatr. Psychiatry* 36.6 (2021), pp. 892–900.
18. Yocum AK, Zhai Y, McInnis MG, and Han P. “Covid-19 pandemic and lockdown impacts: A description in a longitudinal study of bipolar disorder”. In: *J. Affect. Disord.* 282 (2021), pp. 1226–1233.
19. Rush AJ et al. “The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression”. In: *Biol. Psychiatry* 54.5 (2003), pp. 573–583.
20. Schulte-van Maaren YWM et al. “Reference values for major depression questionnaires: the Leiden Routine Outcome Monitoring Study”. In: *J. Affect. Disord.* 149.1-3 (2013), pp. 342–349.
21. Young RC, Biggs JT, Ziegler VE, and Meyer DA. “A rating scale for mania: reliability, validity and sensitivity”. In: *Br. J. Psychiatry* 133 (1978), pp. 429–435.
22. Altman EG, Hedeker D, Peterson JL, and Davis JM. “The Altman Self-Rating Mania Scale”. In: *Biol. Psychiatry* 42.10 (1997), pp. 948–955.
23. Lukasiewicz M et al. *Young Mania Rating Scale: how to interpret the numbers? Determination of a severity threshold and of the minimal clinically significant difference in the EMBLEM cohort.* 2013.
24. De Jong Gierveld J and Van Tilburg T. “The De Jong Gierveld short scales for emotional and social loneliness: tested on data from 7 countries in the UN generations and gender surveys”. In: *Eur. J. Ageing* 7.2 (2010), pp. 121–130.
25. Meyer TJ, Miller ML, Metzger RL, and Borkovec TD. “Development and validation of the Penn State Worry Questionnaire”. In: *Behav. Res. Ther.* 28.6 (1990), pp. 487–495.
26. Antypa N et al. “Associations between chronotypes and psychological vulnerability factors of depression”. In: *Chronobiol. Int.* 34.8 (2017), pp. 1125–1135.

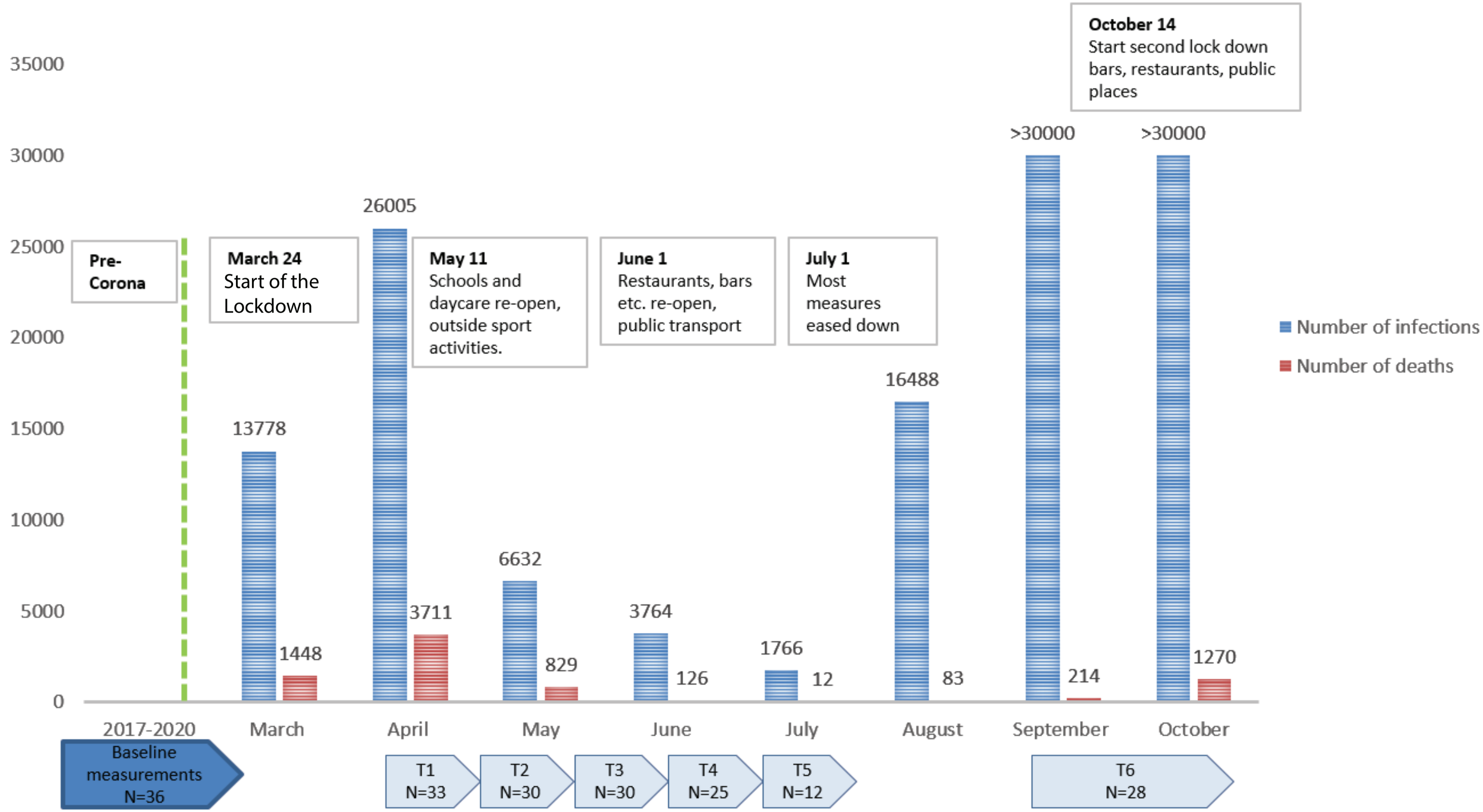
27. Kerkhof AJFM, Hermans D, Figee A, and Laeremans I. “De Penn State Worry Questionnaire en de Worry Domains Questionnaire: eerste resultaten bij Nederlandse en Vlaamse klinische en poliklinische populaties”. In: *Gedragstherapie* 33.2 (2000), pp. 135–145.
28. Heiden C van der, Muris P, Bos AER, and Molen HT van der. “Factor structure of the Dutch version of the Penn State Worry Questionnaire”. In: *J. Behav. Ther. Exp. Psychiatry* 41.3 (2010), pp. 304–309.
29. Cohen S, Kamarck T, and Mermelstein R. “A global measure of perceived stress”. In: *J. Health Soc. Behav.* 24.4 (1983), pp. 385–396.
30. Roberti JW, Harrington LN, and Storch EA. *Further Psychometric Support for the 10-Item Version of the Perceived Stress Scale.* 2006.
31. Lee E.-H. “Review of the psychometric evidence of the perceived stress scale”. In: *Asian Nurs. Res.* 6.4 (2012), pp. 121–127.
32. Hebbrecht K et al. “Understanding personalized dynamics to inform precision medicine: a dynamic time warp analysis of 255 depressed inpatients”. In: *BMC Med.* 18.1 (2020), p. 400.
33. Alloy LB, Nusslock R, and Boland EM. “The development and course of bipolar spectrum disorders: an integrated reward and circadian rhythm dysregulation model”. In: *Annu. Rev. Clin. Psychol.* 11 (2015), pp. 213–250.
34. Noone R et al. “Letter to the Editor: New onset psychosis and mania following COVID-19 infection”. In: *J. Psychiatr. Res.* 130 (2020), pp. 177–179.
35. Uvais NA. “Mania Precipitated by COVID-19 Pandemic-Related Stress”. In: *Prim. Care Companion CNS Disord.* 22.3 (2020).
36. Knight BG, Gatz M, Heller K, and Bengtson VL. “Age and emotional response to the Northridge earthquake: a longitudinal analysis”. In: *Psychol. Aging* 15.4 (2000), pp. 627–634.
37. Geoffroy PA, Bellivier F, Scott J, and Etain B. “Seasonality and bipolar disorder: a systematic review, from admission rates to seasonality of symptoms”. In: *J. Affect. Disord.* 168 (2014), pp. 210–223.
38. Feijt M et al. “Mental Health Care Goes Online: Practitioners’ Experiences of Providing Mental Health Care During the COVID-19 Pandemic”. In: *Cyberpsychol. Behav. Soc. Netw.* 23.12 (2020), pp. 860–864.
39. Fancourt D, Steptoe A, and Bu F. “Trajectories of anxiety and depressive symptoms during enforced isolation due to COVID-19 in England: a longitudinal observational study”. In: *Lancet Psychiatry* (2020).
40. Hetkamp M et al. “Sleep disturbances, fear, and generalized anxiety during the COVID-19 shut down phase in Germany: relation to infection rates, deaths, and German stock index DAX”. In: *Sleep Med.* 75 (2020), pp. 350–353.
41. Dawson DL and Golijani-Moghaddam N. “COVID-19: Psychological flexibility, coping, mental health, and wellbeing in the UK during the pandemic”. In: *J Contextual Behav Sci* 17 (2020), pp. 126–134.
42. Zacher H and Rudolph CW. “Individual differences and changes in subjective wellbeing during the early stages of the COVID-19 pandemic”. In: *Am. Psychol.* 76.1 (2021), pp. 50–62.

43. Kristenson M, Eriksen HR, Sluiter JK, Starke D, and Ursin H. "Psychobiological mechanisms of socioeconomic differences in health". In: *Soc. Sci. Med.* 58.8 (2004), pp. 1511–1522.

44. Stefana A et al. "The COVID-19 pandemic is a crisis and opportunity for bipolar disorder". In: *Bipolar Disord.* 22.6 (2020), pp. 641–643.

45. Hernández-Gómez A, Andrade-González N, Lahera G, and Vieta E. "Recommendations for the care of patients with bipolar disorder during the COVID-19 pandemic". In: *J. Affect. Disord.* 279 (2021), pp. 117–121.

4.6 Supplementary Figures & Tables

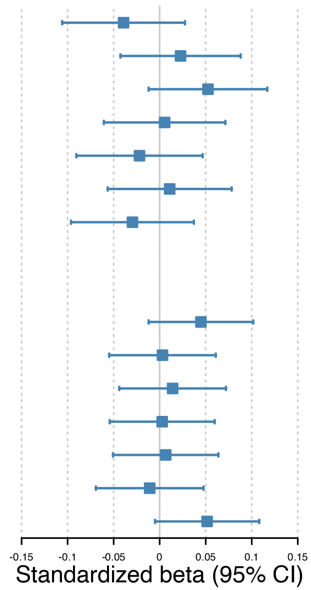


Supplementary Figure 1: Timeline of the study and the development of the COVID-19 pandemic in the Netherlands
Outline of the study measurements and COVID-19 lockdown measures during the study period. Bars indicate the development of COVID-19 pandemic in the Netherlands in terms of infection rates and number of death. The measurements and number of respondents are given below the timeline. T1 to T6 represents the 6 timepoint measurements during the study period.

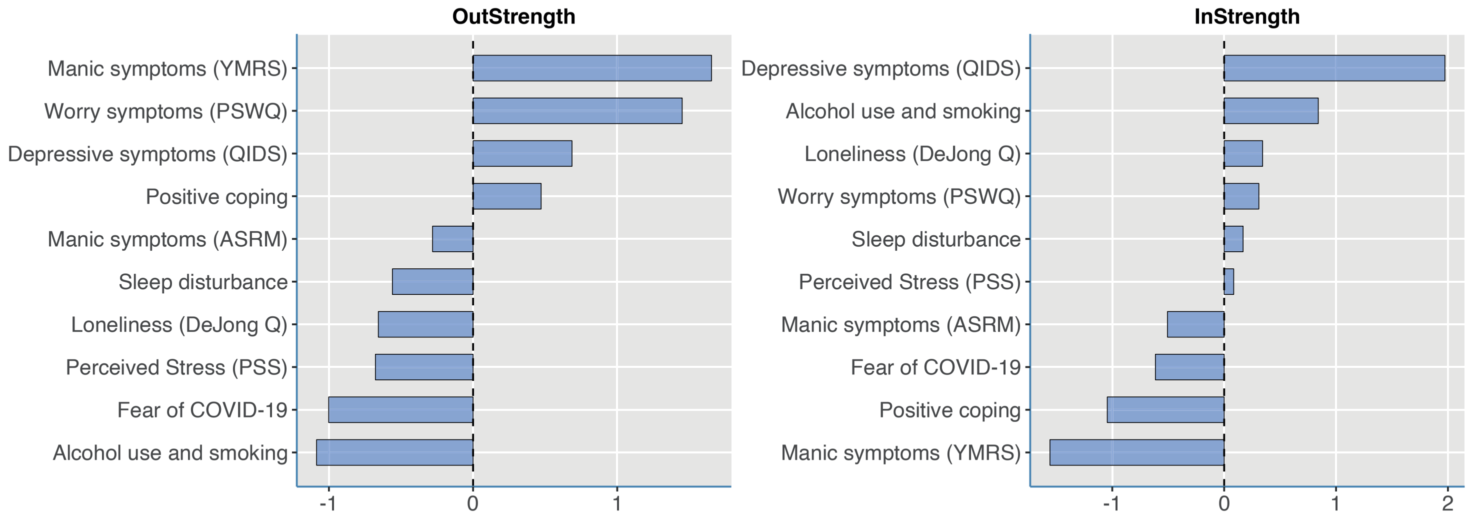
Supplementary Table 1: Stock index DAX. Sleep Med. 2020;75 : 350-353. 41. Dawson DL, Golijani-Moghaddam N. COVID-19 : Psychological flexibility, coping, mental health, and wellbeing in the UK during the pandemic. J Contextual Behav Sci. 2020;17 : 126-134. individual Covid-specific items and Exploratory Factor Analysis results (N = 33). The four dimensions are labelled as 'sleep disturbance', 'fear for COVID-19', 'positive coping' and 'alcohol use and smoking'.

Item (response options: 1=totally disagree – 5=totally agree)	**Factor loading 1**	**Factor loading 2**	**Factor loading 3**	**Factor loading 4**
Because of this period the quality of my sleep is worse	.70	.33	.14	.45
In this period I am having more nightmares	.46	.27	-.20	.31
In this period my daily structure (sleep hygiene, healthy food and sport) has got worsen	.42	.21	-.10	.14
I fear to become infected with corona	.14	.72	.00	-.13
I fear that my loved ones to become infected with corona	-.02	.70	.48	-.24
Because of the threat of the virus I do not leave my home anymore	-.12	.56	-.30	-.19
This period makes me fearful	.37	.55	-.03	.14
Because of the threat of the virus I am anxious of getting close to other people	-.30	.95	.21	-.48
Because of the threat of the virus I am worried about the stability of my mood	.35	.49	-.25	.18
In this period I feel more connected to society	.43	-.04	.47	.07
It is no problem to enjoy myself while being at home more often	-.02	-.13	.75	-.16
I have confidence that the Netherlands will overcome this crisis	-.07	.05	.86	-.09
Despite the virus I stay active (household tasks, gardening, walking, sporting, yoga)	.02	.02	.62	.04
Despite the virus I actively maintain (via phone or online) contacts with friends	-.06	-.05	.53	-.03
Because of corona I have become more active (social media, helping others, more productive)	.40	.15	.56	.29
This period makes me smoke more	.02	-.01	.16	.83
This period makes me drink more alcohol (non-drinker: not applicable)	.11	0.22	-.03	.54
Dimension label	Sleep disturbance	Fear for COVID-19	Positive coping	Alcohol use and smoking
Cronbach's alpha	.60	.81	.79	.70

Predictor of increase	Beta-coefficient	P-value
Manic symptoms (YMRS) trajectory:		
Age	-0.039 (SE: 0.034)	0.25
Female vs male sex	0.023 (SE: 0.033)	0.50
BD type II vs. I	0.052 (SE: 0.033)	0.11
Fear of COVID-19	0.005 (SE: 0.034)	0.87
Positive coping	-0.022 (SE: 0.035)	0.53
Sleep disturbance	0.011 (SE: 0.034)	0.75
Alcohol use and smoking	-0.030 (SE: 0.034)	0.39
Depressive symptoms (QIDS) trajectory:		
Age	0.045 (SE: 0.029)	0.12
Female vs male sex	0.003 (SE: 0.030)	0.92
BD type II vs. I	0.014 (SE: 0.030)	0.63
Fear of COVID-19	0.003 (SE: 0.029)	0.92
Positive coping	0.007 (SE: 0.029)	0.82
Sleep disturbance	-0.011 (SE: 0.030)	0.72
Alcohol use and smoking	0.052 (SE: 0.029)	0.08



Supplementary Figure 2: Predictors for differential changes over time of symptoms trajectory.
Predictors for differential changes over time of (hypo)manic (YMRS) and depressive (QIDS) symptoms trajectory. Data are standardized beta-coefficients of the interaction terms of time ∗ predictor, from univariate mixed models (with time as a continuous variable).



Supplementary Figure 3: In- and out-strength values of (DTW) analysis.
Standardized in- and out-strength values of the direct network plot based on dynamic time warp (DTW) analysis of the time series of 20 BD patients with 4 or more assessments over time[32]. Changes that occur on scales with high outstrength values tend to precede (in time) changes in other scales, whereas scales with high instrength values tend to follow (in time) changes in other scales.

CHAPTER 5

Dynamic time warp analysis of individual symptom trajectories inpatients with bipolar disorder

Mesbah, R., Koenders, M., Spijker, A. T., de Leeuw, M., van Hemert, A. M., & Giltay, E. J. (2023). Dynamic time warp analysis of individual symptom trajectories in patients with bipolar disorder. *Bipolar Disorders*, 66(S1), S578–S579. DOI: 10.1111/bdi.13340

Abstract

Background
Manic and depressive mood states in bipolar disorder (BD) may emerge from the non-linear relations between constantly changing mood symptoms exhibited as a complex dynamic system. Dynamic Time Warp (DTW) is an algorithm that may capture symptom interactions from panel data with sparse observations over time.

Methods
The Young Mania Rating Scale and Quick Inventory of Depressive Symptomatology were repeatedly assessed in 141 patients with BD, with on average 5.5 assessments per patient every 3 to 6 months. DTW calculated the distance between each of the 27∗27 pairs of standardized symptom scores. The changing profile of standardized symptom scores of BD patients was analyzed in individual patients, yielding symptom dimensions in aggregated group-level analyses. Using an asymmetric time-window, symptom changes that preceded other symptom changes (i.e., Granger causality) yielded a directed network.

Results
The mean age of the patients was 40.1 (SD 13.5) years old, and 60% were female. Idiographic symptom networks were highly variable between patients. Yet, nomothetic analyses showed five symptom dimensions: core (hypo)mania (6 items), dysphoric mania (5 items), lethargy (7 items), somatic/suicidality (6 items), and sleep (3 items). Symptoms of the 'Lethargy' dimension showed the highest out-strength, and its changes preceded those of 'somatic/suicidality', while changes in 'core (hypo)mania' preceded those of 'dysphoric mania'.

Conclusion
DTW may help to capture meaningful BD symptom interactions from panel data with sparse observations. It may increase insight into the temporal dynamics of symptoms, as those with high out-strength (rather than high in-strength) could be promising targets for intervention.

5.1 Introduction

Bipolar disorder (BD) is a chronic psychiatric illness with alternating episodes of depression and (hypo)mania[1]. The symptom presentation of BD is heterogeneous, and apparent sub-phenotypes often show a different prognosis, course of illness, and treatment response[2]. Several studies showed that symptomatology, severity, polarity, and cycling patterns of episodes differed strongly between patients with BD[3, 4], whereas recurrent episodes within a patient often seemed to present a similar pattern of symptomatology[5]. In addition, patients with BD (either type I or II) can suffer from rapid cycling, psychosis, and mixed mood episodes[6]. Taking all these together, it is obvious that it is challenging for clinicians to diagnose BD and target interventions for each individual. One of the important aims in the treatment of BD is to identify the individual patterns of so-called prodromal "warning" symptoms and address these symptoms as early as possible to prevent recurrent episodes. Although the clinician and patient try to grasp the individual symptom dynamics in early warning plans, these are often based on retrospective knowledge and subjective interpretations of how a new mood episode could have developed in the recent past. Repeated symptom registrations and analyses of these individual data, might lead to more insight into the individual symptom dynamics and allows for more accurate interventions to prevent new mood episodes.

It is challenging to gain insight into the temporal directional relationships between mood symptoms (either depression or mania), both in individual and in groups of patients with BD. In the majority of studies in BD, sum scores of manic and depressive symptoms with a threshold are used to indicate case status, and life charts are used to register the flux of mood states over time[7]. Moreover, such epidemiological approaches are mostly group-based, and the patterns found may not be applicable to the individual patient[8, 9]. Besides, it is often assumed that BD results from an underlying common cause, but this approach does not take into account that symptoms themselves might also interact and be causally depending on one another in the direction of the relation of certain symptoms[10, 11]. The course of BD is often unpredictable, not because it is random, but because its current behavior depends on a unique path of interactions with the internal and external context. A simple example of this in BD is that lack of sleep in BD often leads to increased energy and/or activity, which in its turn leads to more lack of sleep. BD can be approached as a complex dynamic system[12, 13] in which there are complex dependencies in time between constantly changing components (such as mood symptoms and environmental factors), across multiple levels of organization and scale. These components together form the behavior of the whole, such as manic, euthymic, and depressive mood states, as emergent phenomena.

Dynamic time warp (DTW) is a computational algorithm that could be used to process individual symptom data and takes account of potential non-linear dynamics among symptoms and focuses on change profiles rather than absolute levels of symptom scores[14, 15]. This method is a widely used statistical algorithm[16], but not in the field of psychiatry and psychology[15]. This method helps us to investigate the symptom interconnection within panel data, also when there are only a parse number of time points. It starts with analyzing individual patient data (i.e., idiographic approach, individual level) after which these are aggregated (i.e., nomothetic analysis, group level). This is important as BD is a multicausal, dynamic, and idiosyncratic disorder, for which personalized approaches are needed to target those symptoms that directly affect other symptoms[11, 17, 18]. The symptom network approach can help to analyze and visualize the interconnection of symptoms, which may explain the switching of mood states[19]. Sudden switches between relatively stable mood states are referred to as critical transitions, catastrophic phenomena, or tipping points in the field of complex systems[11, 13, 20]. In addition, using this network approach, it will be possible to provide patients with their own unique symptoms profile which enables them and their caregivers to gain more insight into their symptom dynamics.

So far, DTW has only been used to study unipolar depression[14, 15, 20, 21], but no study has focused solely on BD. To our best knowledge, only two cross-sectional network studies examined the mood symptoms in BD.[22, 23] The first study[22] studied 195 BD patients and participants at high risk and found that symptoms were most strongly interrelated with symptoms at the same mood pole, and the most central symptoms among the BD network were symptoms measuring the level of energy or activity. In the second study,[23] 125 patients with BD were allocated into three longitudinal clinical courses (minimally impaired, depressed, and cycling). Their results showed that in severe courses of illness the mood symptoms were most strongly interconnected. These two studies had cross-sectional designs, meaning that the temporal dynamics of symptoms were not investigated.

In the current study, we use DTW to analyze the dynamics of symptoms over time in the patient sample previously used for the cross-sectional network analysis[23]. In this study, we utilized symptoms of BD repeatedly (every 3 to 6 months) to assess depression and manic symptoms in 141 patients with BD. We aimed to present the first implementations of DTW time-series analysis on BD symptoms trajectories. Both individual level (i.e., idiographic) and group level (i.e., nomothetic) analyses are presented.

5.2 Method

5.2.1 Study sample

Data were derived from a 2-year longitudinal study among 181 adult bipolar outpatients, with a diagnosis of BD I or BD II (based on DSM-IV), who were treated by the Outpatients Clinic for Mood Disorders in the Hague (the Netherlands). The exclusion criteria were schizo-affective disorder, neurological diseases, and substance abuse disorder. All participants signed the written informed consent before enrollment and the study was approved by the Medical Ethical Committee Mental Health Care Organizations Rotterdam (number 7220) and the Central Committee Human Studies (number NL18286.097.07). The study design of this cohort has been described previously[23].

5.2.2 Measurements

For the current study only data of mood assessments of depressive and manic symptoms were used. These two measurements were assessed at baseline and subsequently every 3 to 6 months yielding up to 6 measurement points (at baseline, 6, 12, 18, 21, and 24 months) per participant.

Depressed symptoms
Depressive symptoms were assessed by the 16 items Quick Inventory of Depressive Symptomatology (QIDS-SR)[24]. Each item is rated 0-3. The QIDS-SR total score ranges from 0 to 27, with scores of 5 or lower indicative of no depression, scores from 6 to 10 indicating mild depression, 11 to 15 indicating moderate depression, 16 to 20 indicating severe depression, and total scores greater than 21 indicating very severe depression. This self-report questionnaire has good internal consistency (Cronbach's alpha > 0.86). Cronbach's alpha in the current study was 0.80 at baseline.

Manic symptoms
For the assessment of manic symptoms, the clinician-rated, 11-item Young Mania Rating Scale (YMRS)[25] was used. The items are rated based on the patient report and the clinical impression of the interviewer. There are four items rated 0-8 (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are rated 0-4. The YMRS total score ranges from 0 to 60 with scores from 13 to 19 indicating minimal symptoms, 20 to 25 indicating mild mania, 26 to 30 indicating moderate mania and 38 to 60 indicating severe mania. The YMRS has good inter-rater reliability (r=.93).[25] Internal consistency (Cronbach's alpha) in the current sample was 0.79 at baseline.

5.2.3 Statistical analysis

Sociodemographic and clinical variables at baseline are summarized as means and standard deviations (SD) or percentages, as appropriate.

Time-series panel data were gathered, which consisted of 27 depressive and manic symptom ratings assessed on the same time scale. Participants who had 3 or less of the mood assessments were excluded, which resulted in 141 participants who were included in the current analyses. When we compared these 141 participants with 38 having 3 or fewer assessments, no significant differences were found in terms of age or gender (p-value for age 0.73; for gender 0.56).

DTW was used to assess the similarity of symptom dynamics within participants, both in undirected and directed (in time) analyses. When the trajectories of the severity of a symptom pair showed large similarities, the resulting distance will be small, whereas when these changes over time are rather erratic and independent, their distance will be large. DTW is thus a shape-based time-series clustering technique. All item scores were group-level standardized before the analyses, in order to let the results be based on the relative changes over time.

Within each patient (i.e., idiographic approach), we used DTW to calculate each "distance" between each pair of symptoms, based on the optimum warping path between two series under certain constraints, as described in detail in Figure 5.1. For the undirected analyses, this resulted in a 27 by 27 symmetric distance matrix for each individual. A low distance represents a time series of item scores that are very similar, whereas a high distance represents dissimilar item dynamics over time. The time window was set at 1, meaning that similar changes between t-1, t, and t+1 were taken into account. A dissimilar score at the start and end of each time series could have a disproportional effect on the total distance because these cannot be dynamically aligned. Therefore, interpolation of 5 values between each time point was applied before calculating the distance, which subsequently reduced the disruptive effect of starting and endpoints mismatches. Moreover, there is a tendency of scores that remained zero throughout follow-up to cluster strongly together, therefore for each pair of symptoms that scores zero on each time point we added a penalty of distance 1 to the final distance of that symptom pair in that participant. This patient level analysis resulted in 141 individual distance matrices.

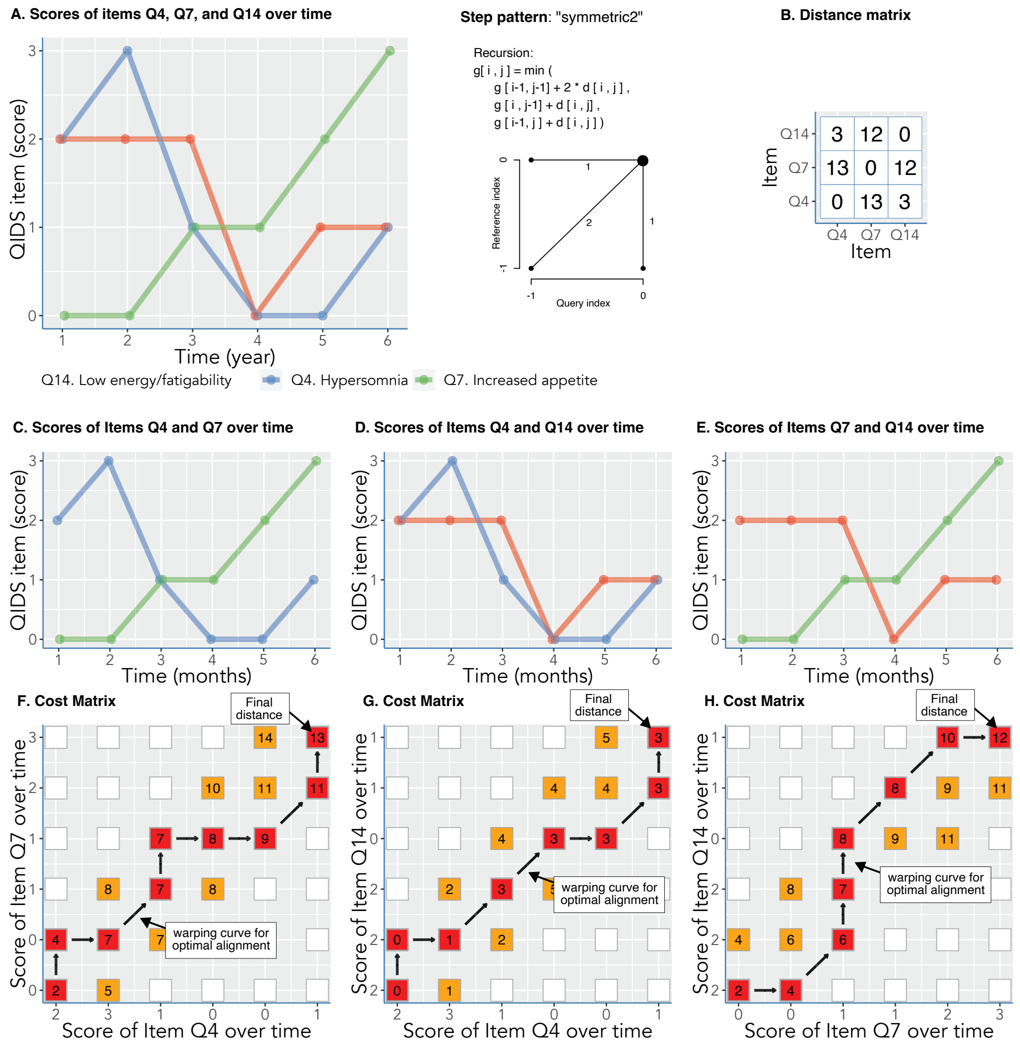

A. Scores of items Q4, Q7, and Q14 over time
QIDS item (score)
Time (year)
Q14. Low energy/fatigability
Q4. Hypersomnia
Q7. Increased appetite
Step pattern: "symmetric2"
Recursion:
g[i , j] = min (
g [i-1, j-1] + 2 * d [i , j] ,
g [i , j-1] + d [i , j] ,
g [i-1, j] + d [i , j])
Reference index
Query index
B. Distance matrix
Item
C. Scores of Items Q4 and Q7 over time
D. Scores of Items Q4 and Q14 over time
E. Scores of Items Q7 and Q14 over time
Time (months)
F. Cost Matrix
G. Cost Matrix
H. Cost Matrix
Final distance
warping curve for optimal alignment
Score of Item Q7 over time
Score of Item Q14 over time
Score of Item Q4 over time
Score of Item Q7 over time

Figure 5.1: Explanation of the dynamic time warp analysis (DTW), an algorithm for measuring similarity between two time series. We analyzed three QIDS symptom scores over time. In panel [A] the (unstandardized) scores of these individual items are given over time during the follow-up. We used the shape-based time-series clustering technique of DTW, to yield the distance as a dissimilarity measure. It aims to find the optimum warping path between two time series. The first step in DTW involves creating a local cost matrix (LCM), which has 6 × 6 dimensions (as we had 6 assessments in time). In the seconds step, the DTW algorithm finds the path that minimizes the alignment between the two item scores by iteratively stepping through the LCM, starting at the lower left corner (i.e., LCM[1, 1]) and finishing at the upper right corner (i.e., LCM[6, 6]), while aggregating the total distance (i.e., 'cost'). At each step, the algorithm takes the step in the direction in which the cost increases the least under the chosen constraint. The constraint was the Sakoe-Chiba window of size one, with one time-point before and after the current assessment. The way in which the algorithm traverses through the LCM is dictated by the chosen step pattern, in our case the default "symmetric2" step pattern [B]. Parts [C], [D], and [E] explain the calculations of dynamic time warp distances for the three symptom pairs, yielding 10, 8, and 1 as for their respective distances. We can conclude that the green and red lines show a more similar route over time (with a distance of only 3), which is represented by the smaller distance compared to each distance with the red line (with distances of 10 and 8).

The 141 individual distance matrices were subsequently analyzed on the group level (i.e., nomothetic approach), through a Distatis three-way principal component analysis[26]. The Distatis analysis yielded principal components that are called compromise factors, of which the first three explain the largest amount of variance (used as x, y, and z in the 3-dimensional supplementary plot). These compromise factors thus best describe the similarity structure of the 141 distance matrices. The compromise factors were used as coordinates of the 27 symptoms as points such that the distances in the map best reflect symptoms covarying with its nearest neighboring symptoms[27]. The first against the second, and the first against the third compromise factors were plotted into the x-y planes, and the three compromise factors were also plotted in a supplemental three-dimensional interactive plot.

A hierarchical cluster analysis was applied according to 'Ward.D2' clustering methods, which was visualized in a dendrogram. Ideally, all items of the same dimension are similar to each other but are as dissimilar as possible from items in a different dimension. To estimate the optimal number of dimensions, elbow and silhouette plots were used. The elbow can be observed as a sharp change in the slopes of adjacent line segments, which location might indicate a good number of dimensions to retain. The silhouette method calculates the average distance of each item to the items in the same dimensions as well as the average distance to the items in the nearest cluster, with a plot of the average scores over all items against a different number of dimensions. The number of dimensions yielding the highest average silhouette score is the best number of dimensions[28].

For the directed analyses of symptom dimensions scores, the same DTW algorithm was used as for the undirected analyses, except for a crucial difference. The window type using the Sakoe-Chiba band[16] was specified as being asymmetric, such that the flow of information was assessed in one direction, from dimension 1 to dimension 2, but not vice versa. For each of the 141 patients, a directed distance matrix was calculated for the standardized sum scores of the 5 dimensions. A directed network plot was plotted from the resulting distance matrix that was the average of the 141 directed distance matrices. Two standardized metrics of node centrality were derived: in-strength centrality and out-strength centrality. The directed edges are represented by arrows, with tips pointing in the temporal direction (which is a prerequisite for a causal relationship). Out-strength centrality refers to the number and strengths of outgoing edges that depart from a specific node (i.e., in our DTW analysis an item with a high out-strength score implies that item changes tend to precede changes in other item scores). In-strength centrality refers to the number and strengths of incoming edges of a specific node (i.e., in our DTW analysis an item with a high in-strength score implies that its changes tended to follow upon changes in other item scores).

To assess whether our undirected analyses yielded reliable results, we did a random split on the data and repeated the analyses in both subsets. This helped us to determine whether this resulted in similar findings or discrepant results, which may signal unreliable findings. Node placement was done by using the Procrustes algorithm (from the R package 'networktools'), to aid the visual comparison between the two networks. This was only available for undirected analyses using symmetric distance matrices. The congruence coefficients (with the 2.5th and 97.5th percentiles) were estimated, through bootstrapping of 200 random splits of the 141 participants. A value below 0.85 indicates poor similarity, a value in the range of 0.85 to 0.94 indicates fair similarity, and a value of 0.95 can be considered as being equal[29].

Descriptive analyses were done with SPSS version 25 (IBM Corp Released 2017, IBM SPSS Statistics for Windows, Version 25). Network analysis were done with the packages "dtw" (version 1.22-3), "parallelDist" (version 0.2.4), "qgraph" (version 1.6.9), “stats" (version 4.0.3), "networktools" (version 1.2.3), and the ’plotly’ package (version 4.9.4.1) for the R statistical software (R version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.r-project.org/). A sample R script for the DTW analyses is provided as supplementary material and can be downloaded here: https://osf.io/6nmtk.

5.3 Results

The baseline characteristics of the 141 patients are shown in Table 5.1. The mean age was 49.1 years with a standard deviation (SD) of 13.5. The majority of the patients were female (60%). The mean score of baseline QIDS and YMRS were 7.9 (SD 5.1) and 1.8 (SD 3.2), respectively, indicating mild depressive symptoms and no manic symptoms. This is due to the fact that most patients were euthymic at study entry.

5.3.1 Individual patient analyses (idiographic approach)

We used DTW clustering method to analyze data from each participant. Here, only three exemplar patients were selected from the full data-set, to demonstrate how DTW can be applied on the individual patient level (Figure 5.2 for patients A, B, and C). These three patients show a high degree of inter-individual variability in their symptom trajectories. In patient A there was a tight clustering of mania symptoms, whereas in patient B there was a tighter clustering of depressive symptoms. Patient C showed two separate symptom dimensions, one of the depressive symptoms later transitioning into one of the manic symptoms.

Patient A was a 51-year-old female (bipolar disorder type I) with onset of depression at 37 years and onset of mania at 41 years of age. Her dendrogram shows a prominent clustering of mania symptoms. In assessments 2 and 3 'pressured speech' was her most prominent symptom. The network graph shows that changes in symptoms of 'dysphoric mania' (blue symptoms) and 'core (hypo)mania' (red symptoms) and a few of 'somatic/suicidality' (purple symptoms) were mostly in phase over time. Most symptoms of 'lethargy' (green symptoms) were only loosely connected to her symptom network.

Patient B was a 60-year-old female (bipolar disorder type II) with onset of depression at 20 years and onset of hypomania at 26 years of age. Her dendrogram shows a more prominent clustering of depressive symptoms, starting with high ratings on 'sad mood', later followed by higher ratings of 'Psychomotor agitation' and 'Mid-nocturnal insomnia'(see Figure 5.2B.B). She had very low ratings for YMRS items measuring the (hypo)manic symptoms, several items of YMRS could not be included in her Dendrogram, because ratings remained zero throughout follow-up. Her individual network graph demonstrated the similarity of changes over time only for the symptoms of 'somatic/suicidality' (purple symptoms) and 'lethargy' (green symptoms).

Patient C was a 59-year-old female (bipolar disorder type I) with late-onset mania at 39 years of age and late-onset depression at 49 years . Her dendrogram shows a relatively stronger clustering of symptoms than patients A and B. Symptoms with the highest severity scores at the first 3 assessments were 'mid-nocturnal insomnia' (orange symptoms) and 'poor concentration/indecisiveness' (green symptoms). Later, the strongest connections were between symptoms of 'core (hypo)mania'.

5.3.2 Group-level analysis (nomothetic approach)

The nomothetic analysis of the 141 patients is shown in Figure 5.3. The elbow and silhouette plots indicated that five dimensions fitted the data best, mainly based on the average silhouette score (Figure 5.3A). The results of dendrogram hierarchical cluster demonstrated five dimensions of symptoms (see Figure 5.3B). These were based on all 27 individual items were: (1) core (hypo)mania (6 items: 'pressured speech', 'irritability', 'elevated mood', 'increased activity/energy', 'low need for sleep and fast thought content'), (2) dysphoric mania: (5 items: 'content/delusions/hallucinations', 'poor insight', 'aggressive behavior', 'poor appearance', 'high sexual interest', (3) lethargy (8 items: 'low self-esteem/guilt', 'low interest', 'psychomotor slowing', 'psychomotor agitation', 'hypersomnia', 'sad mood', 'poor concentration/indecisiveness', 'low energy/fatigability'), (4) somatic/suicidality (6 items: 'decreased appetite', 'Increased appetite', 'suicidal ideation', 'increased weight', 'early morning insomnia', 'decreased weight') and (5) sleep: (2 items: 'sleep onset insomnia', 'mid-nocturnal insomnia').

The results of three-way principal component Distasis analysis on the 141 distance matrices revealed in three principal components or 'compromise factors'. These explained 28.5%, 14.1%, and 10.2% of the variance. In a three-dimension interactive plot, a more similar change over time among patients is represented by a smaller distance between symptoms (i.e., their relative distance in the compromise space, Supplementary Figure 5.1: download here: https://osf.io/z4upr). The two compromise plots (of the first against the second compromise factor in Figure 5.3C, and of the first against the third compromise factor in Figure 5.3D demonstrate the spread of the 27 items, and show the particular strong clustering of the symptoms that were included in dimensions 1 and 2 (i.e., 'core hypomania' and 'dysphoric mania').

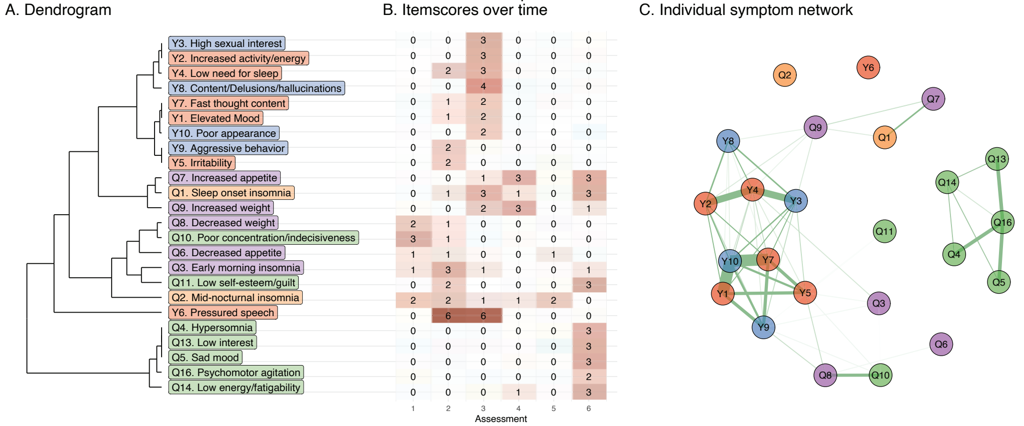
Next, a directed network was created for the changes in scores of the 5 symptom dimensions (Figure 5.4). The directed network plot showed that changes in 'core (hypo)mania' tended to precede similar changes in 'dysphoric mania', and that changes in 'lethargy' tended to precede similar changes in 'somatic/suicidality'. Dimensions 3 and 1 (i.e., 'lethargy' and 'core (hypo)mania') had the strongest out-strength centrality scores relative to the other three dimensions. Dimensions 4 and 2 (i.e., 'somatic/suicidality' and 'dysphoric mania') had the strongest in-strength centrality scores relative to the other three dimensions.

Finally, in order to validate our results of 5 symptom dimensions, we randomly split our sample of 141 patients into two samples of 70 and 71 patients. The analysis of both samples confirmed the stability of the five symptoms dimension (Figure 5.5). The median congruence coefficient was very high at 0.984 (2.5^{th} and 97.5^{th} percentiles of values) when we bootstrapped the random split procedure 200 times), supporting the high reliability of the 5 nomothetic symptom dimensions across patients.

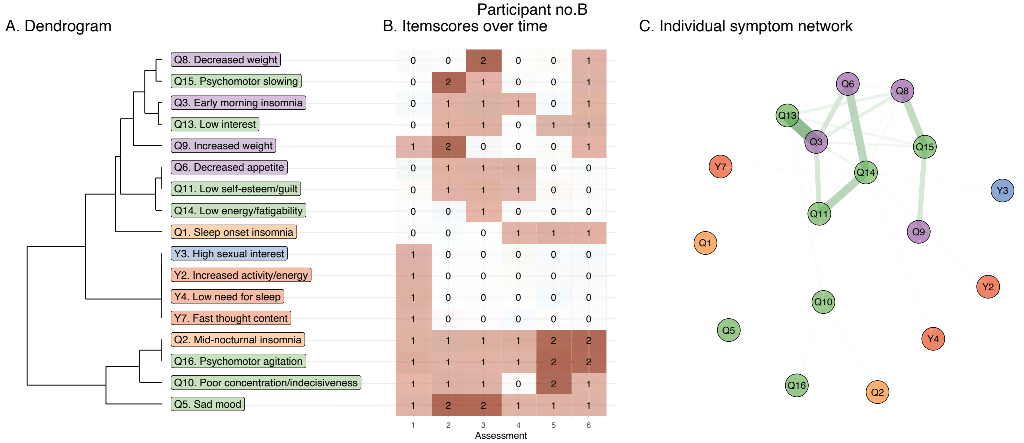
Table 5.1: Baseline sociodemographic characteristics in 141 participants with bipolar disorder.

	(N=141)
Sociodemographic characteristics:	
Male, sex; n (%)	53 (37.6%)
Age; mean (SD)	49.1 (11.7)
Level of education: n (%)	
- Primary	29 (20.6%)
- Secondary	46 (32.6%)
- Higher	66 (46.8%)
Current smoker; n (%)	60 (42.6%)
Drugs use; n (%)	10 (7.1%)
Alcohol use; n (%)	
- none	45 (31.9%)
- 1-2 units/day	79 (56.0%)
- $\geq$ 3 units/day	15 (10.6%)
Clinical characteristics:	
Bipolar disorder type 1; n (%)	102 (72.3%)
Age of onset; mean (SD)	
Age of onset first (hypo-) mania	29.7 (10.4)
Age of onset first depression	27.0 (10.1)
QIDS baseline; mean (SD)	7.9 (5.1)
YMRS baseline; mean (SD)	1.8 (3.2)
Medication use baseline: n (%)	
- Lithium	100 (70.9%)
- Anti-epileptics	29 (20.6%)
- Anti-psychotics	36 (25.5%)
- Benzodiazepines	42 (29.8%)
- Antidepressants	51 (36.2.0%)

Participant no.A



Participant no.B



Participant no.C

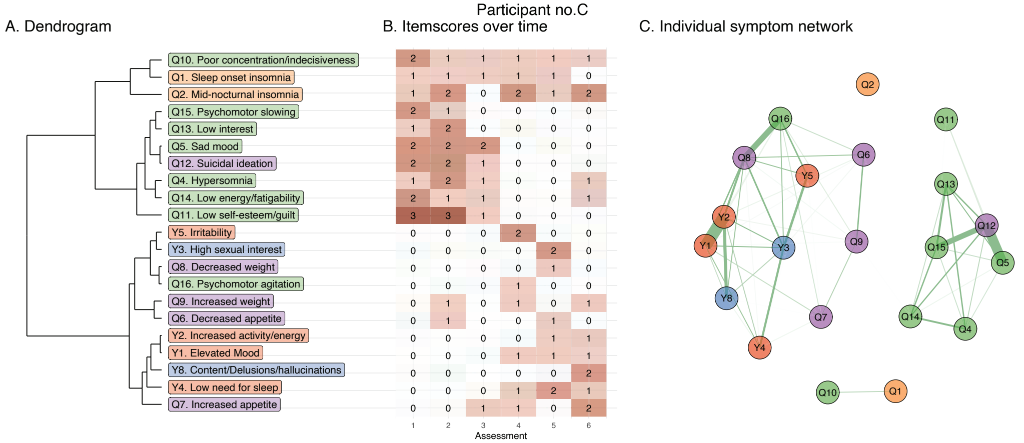


Figure 5.2: Idiographic DTW analysis in three participants (patient A, B and C). Panels A shows the dendrogram of the clustering of symptoms with more similar trajectories over time (with the symptoms colored according to the nomothetic symptom dimensions), panels B shows the raw item scores over time every 3 to 6 months (with the severity being color coded), and panel C shows the individual symptom networks based on their DTW analysis. These samples analyses were done using unstandardized item scores to simplify the interpretation of these illustrations, whereas all other analyses were done using group-level standardized symptoms scores.

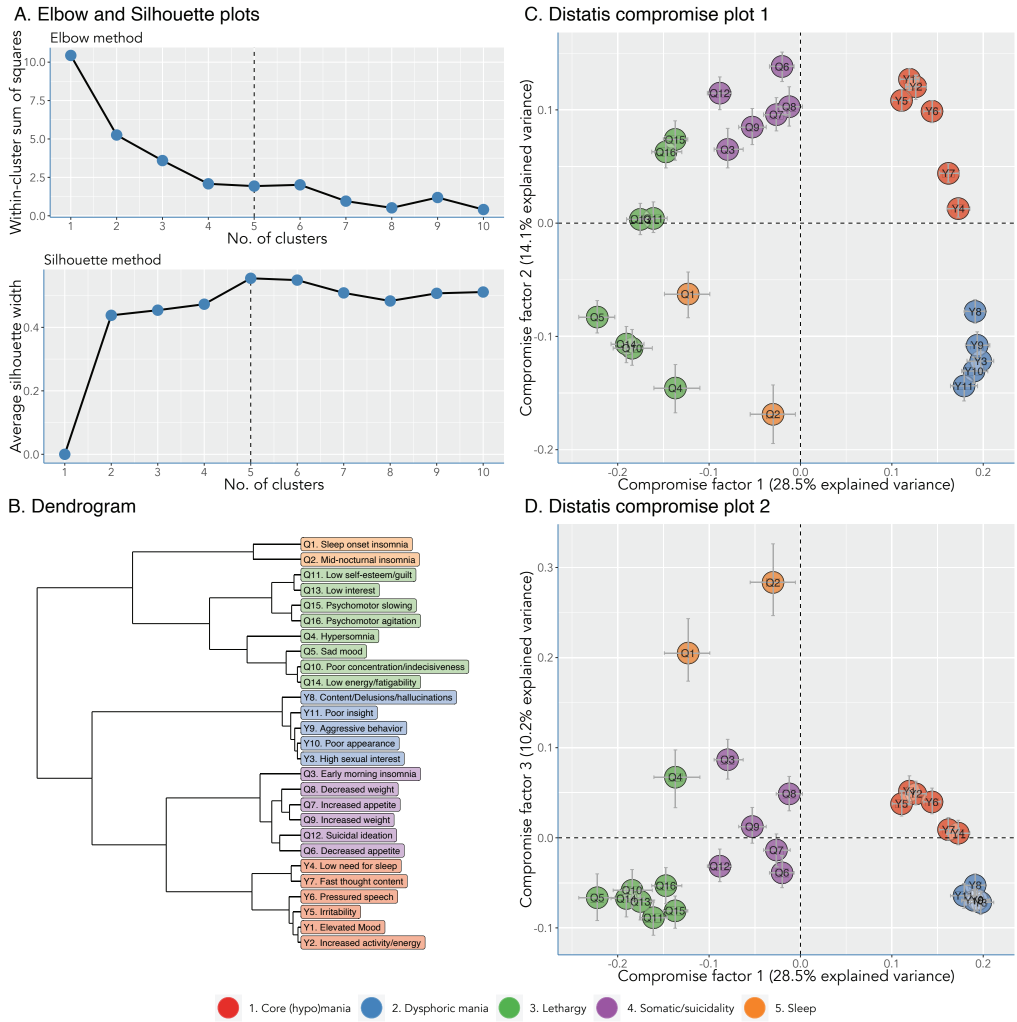


Figure 5.3: Nomothetic analyses based on all distance matrices from 141 participants. [A] A scree plot based on the elbow and silhouette method indicated five symptom dimensions. [B] A dendrogram was created, based on the Ward's (D2, i.e., general agglomerative hierarchical clustering procedure) clustering criterion on the compromise factors of the Distatis analysis of 141 distance matrices. [C] The Distatis analysis yielded three compromise factors. The position of each of the 27 BD items are shown in x-y scatter plot of the compromise space according to the first and second compromise factors, and [D] the first and third compromise factors. Error bars represent the 2.5 th and 97.5 th percentile values, derived from 500 bootstrapping resamplings.

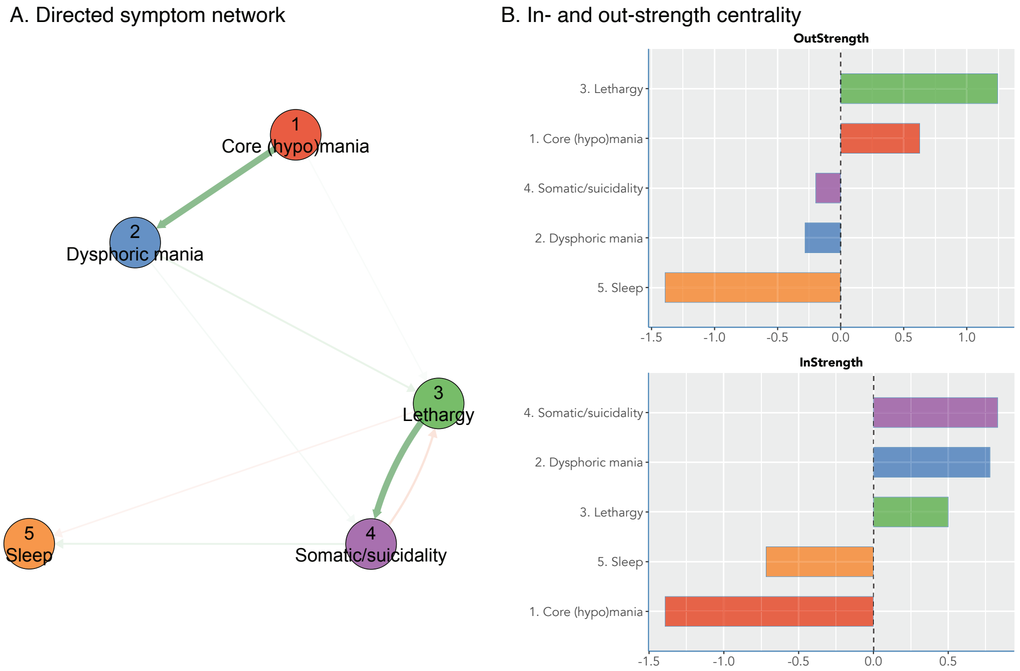


Figure 5.4: Directed symptom network in 141 BD patients. In a directional network, the flow of information is in one direction, from one node to another. The edge thickness represent the median value of the strength of the temporal associations among symptoms. Dimensions 'lethargy' and 'Core (hypo)mania had the strongest out-strength levels, whereas 'somatic/suicidality' and 'dysphoric mania' the strongest in-strength.

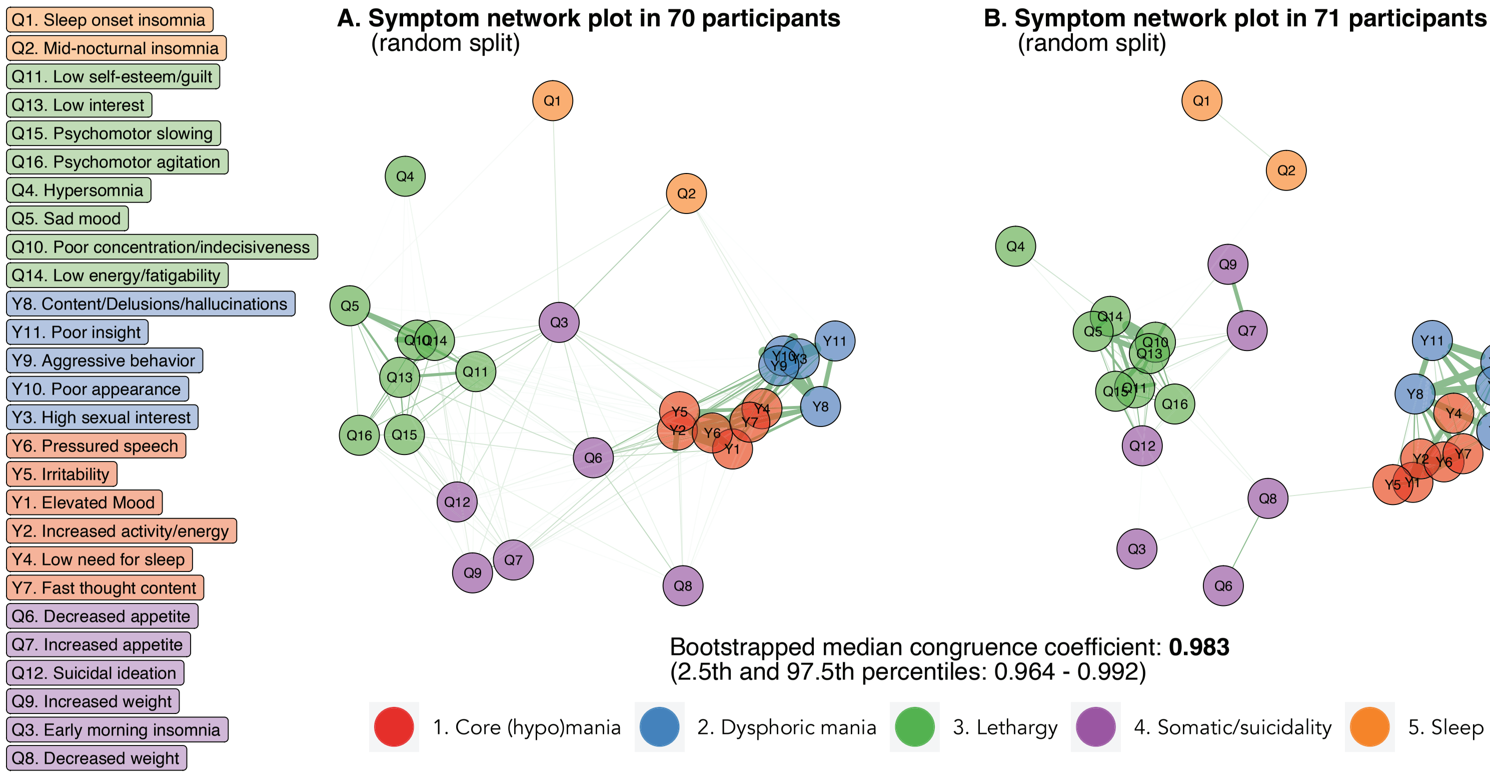


Figure 5.5: Network plots of two subsamples [A and B] of the 141 patients. We used an automated random split with a subset of 70 and 71 patients each, in which we conducted separate DTW analyses. Node placement was done by using the Procrustes algorithm (from the R Package 'networktools'), to aid the visual comparison between the two networks. The congruence coefficient through 200 random splits was high, with a median of 0.984 (2.5^{th} and 95^{th} percentiles: 0.967-0.993).

5.4 Discussion

The current study is the first to analyze a time series of depression and manic symptoms using DTW analyses in patients with BD. We studied interactions and relative changes in symptom severity within and between participants. Overall, the results of our individual patient analyses showed substantial variability between patients. Despite this individual variability, our group-level analyses revealed 5 symptom dimensions (core [hypo]mania, dysphoric mania, lethargy, somatic/suicidality, and sleep). The identification of these 5 symptom domains acknowledges the variability of clinical states that fall within the bipolar syndrome, which is much more complex than simply being either manic or depressed. The five symptom dimensions (core [hypo]mania, dysphoric mania, lethargy, somatic/suicidality, and sleep) that were identified through the group-level analyses, are robust since the clustering in two samples after a 200 random sample split-check analyses showed a large congruence factor. Moreover, we were able to analyze the temporal dynamics between these symptom dimensions as well. Below we will describe in more detail the clinical validity and implications of these findings.

The symptom cluster 'core (hypo)mania' seems to reflect the 'classical' manic state with increased energy, overactivity, and euphoric mood. This is in line with a recent network analysis showing that symptoms of core (hypo)mania were the most interconnected symptoms in the manic network.[30] The 'dysphoric mania' domain typically reflects what has previously been described as a mixed manic mood state,[31, 32] in which energy is high, but mood is characterized by irritation and agitation. Previous factor analyses also report both a 'pure' manic and a dysphoric factor[33, 34] in line with our findings. However, in the current study, the dysphoric domain also contains psychotic features. This specific combination resembles what Himmelhock, Coble, Kupfer, & Ingenito, 1976 described decades ago as an 'agitated psychotic depression in a small group of BD patients. The authors hypothesized that this psychiatric state represents a transitional period when the patient switches from depression to mania or vice versa but becomes 'trapped' in the 'switch' state. Also in a more recent review, it is implicated that approximately 20-30% of patients with BD may present mixed symptom states when transitioning from mania to depression or vice versa[35]. With the current data and analysis technique, we found evidence that this hypothesis might be correct. Indeed, the 'dysphoric manic state' seems to temporally follow the 'core (hypo) manic' mood state, implicating that the manic state tends to transitions into a mixed state over time. This also implies that the opposite direction could occur, when pure manic symptoms drop, dysphoric symptoms will drop subsequently. Clinically this means that in order to prevent a dysphoric state, manic symptoms should be diminished at an early stage. But also, once the patient is in a dysphoric state the interventions might preferably be anti-manic and not anti-depressant, in order to decrease the severity of the dysphoric state. This is in line with existing evidence that antidepressants (especially as monotherapy) during a mixed state could increase the severity of this state[36, 37].

Two other symptom domains that were found in our sample, seem to be positioned in the 'depressive pole', which are 'lethargy' and 'somatic/suicidality. 'Lethargy' consists of typical depressed symptoms (e.g., guilt, low interest, lack of energy, inactivity, hyposomnia). This seems to be in line with previous research, showing consistently 'sad mood' and 'low energy/fatigue' as the most central symptoms in depressive networks in patients with BD[22, 23, 38, 39]. This domain also resembles the factor 'inhibited depression' as found by[40]. The 'inhibited depression' factor also typically lacked symptoms reflecting suicidality and was even associated with lower suicide rates. Similarly, in the current sample, suicidality falls into another cluster, in this case, the 'somatic/suicidality' dimension which importantly seems to overlap with the symptoms of a melancholic depression (changes in appetite, psychomotor slowing, early morning insomnia, and suicidality). The temporal dynamics between these dimensions in our an analysis shows that the 'lethargy' mood state with inactivity and feelings of guilt tends to precede increases in symptom severity in the somatic/suicidality mood state. Again, this also implies that decreases in the 'lethargy' domain tend to be followed by decreases in the somatic/suicidality domain, implicating that treatment might be focused on the 'lethargy' symptoms rather than 'somatic/suicidality' symptoms, in order to decrease the severity of either mood state.

Lastly, we found a separate insomnia domain in the current data, that appeared to be rather unrelated to the other mood domains. This is surprising, given the fact that sleep is such a central symptom of BD. A previous DTW analysis from our group also revealed a separate sleep dimension in patients with depressive episodes (Hebbrecht et al). This should not necessarily mean that sleep does not play an important role in bipolar disorder mood regulation, as it is possibly not specifically related to a specific mood state. Previous studies show that even during euthymia sleeping problems can remain present in a majority of the BD patients[41] which explains why sleep is not specifically related to the increase and decrease of the other symptom cluster in our sample. It might even imply that these symptoms are rather chronic in nature.

A major strength of the current study is that it provides insight in temporal dynamics of BD symptoms using time series, while many other clustering techniques focus on static cross-sectional analyses. It shows that DTW is a promising method that allows clinicians and patients to depict which change in dimension precedes that of which other dimension. It may help the clinicians in decision-making and personalized treatment. The individual-level analysis may eventually help to identify early warning symptoms of an episode in the treatment, when the number of assessments is large enough to detect consistent dynamics. The symptoms with the highest out-strength score could perhaps be targets in personalized treatment in order to prevent a more severe mood state. For instance, if a patient has central symptoms with the highest scores on 'early morning insomnia' and 'sad mood', these two symptoms could be primarily targeted in the intervention as these symptoms potentially could develop into other symptoms, resulting in a more severe episode. Another strength of this study is that we introduced individual-level as well as group-level analysis, whereas all previous studies analyzed static cross-sectional data on the group level only[42].

There are also some limitations that need to be discussed. The time intervals between assessments were long (3 to 6 months), and only up to 6 assessments were done per patient. Future studies could explore whether shorter intervals between assessments would yield similar symptom dimensions and centrality. Yet, many BD patients with a current episode may be incapable to complete daily or even weekly assessments. The co-occurrence of symptom dynamics that we have found in this study was however highly reliable among participants as illustrated by the high congruence factor and its tight confidence interact, and should therefore be considered as global BD symptom dimensions.

Finally, symptom scores are subjective, as they depend on the person's ability to correctly read their internal emotional states.

In sum, our patient-level analyses could be used to visualize a personalized profile of the dynamic relationship between the individual symptoms. This might help the clinicians and the patients to better understand individual patients' characteristic interaction of symptoms[43, 44, 45] A personalized approach might be important, as the idiographic findings tended to be highly variable between patients. DTW may be used for the detection of the central symptoms of one individual patient. Our group-level analysis underlines the variability of clinical states of the bipolar syndrome, which appears much more complex than the two poles of either mania or depression. Nevertheless, replication of the current study with shorter time intervals is recommended for future studies, in which also the influence of environmental factors could be incorporated (e.g., life events, changes in psychotropic medication, and lifestyle factors). Moreover, as we DTW analyses of symptom time series may only indicate only Granger causality, experimental designs are necessary to assess the clinical utility of targeting specific treatments at symptoms with high out-strength centrality. Whether patient-level analyses are of clinical value to more precisely target customized treatments should also be explored further.

Bibliography

1. Judd LL et al. "The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders?" In: *J. Affect. Disord.* 73.1-2 (2003), pp. 19–32.
2. Peters AT et al. *Symptom Dimensions and Trajectories of Functioning Among Bipolar Youth: A Cluster Analysis.* 2018.
3. Sentissi O et al. "Predominant polarity in bipolar disorder patients: The COPE bipolar sample". In: *J. Affect. Disord.* 250 (2019), pp. 43–50.
4. Uher R, Mantere O, Suominen K, and Isometsä E. "Typology of clinical course in bipolar disorder based on 18-month naturalistic follow-up". In: *Psychol. Med.* 43.4 (2013), pp. 789–799.
5. Kessing LV, Hansen MG, et al. "The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders–a life-long perspective". In: *Acta Psychiatrica* (2004).
6. Phillips ML and Kupfer DJ. "Bipolar disorder diagnosis: challenges and future directions". In: *Lancet* 381.9878 (2013), pp. 1663–1671.
7. Koenders MA, Nolen WA, Giltay EJ, Hoencamp E, and Spijker AT. "The use of the prospective NIMH Life Chart Method as a bipolar mood assessment method in research: A systematic review of different methods, outcome measures and interpretations". In: *J. Affect. Disord.* 175 (2015), pp. 260–268.
8. Fried EI. "Problematic assumptions have slowed down depression research: why symptoms, not syndromes are the way forward". In: *Front. Psychol.* 6 (2015), p. 309.
9. Borsboom D, Mellenbergh GJ, and Heerden J van. "The theoretical status of latent variables". In: *Psychol. Rev.* 110.2 (2003), pp. 203–219.
10. Fried EI and Nesse RM. "Depression sum-scores don't add up: why analyzing specific depression symptoms is essential". In: *BMC Med.* 13 (2015), p. 72.
11. Borsboom D et al. "Network analysis of multivariate data in psychological science". In: *Nature Reviews Methods Primers* 1.1 (2021), pp. 1–18.

12. Olthof M, Hasselman F, and Lichtwarck-Aschoff A. “Complexity in psychological self-ratings: implications for research and practice”. In: *BMC Med.* 18.1 (2020), p. 317.

13. McNally RJ. “Network Analysis of Psychopathology: Controversies and Challenges”. In: *Annu. Rev. Clin. Psychol.* 17 (2021), pp. 31–53.

14. Hebbrecht K et al. “Understanding personalized dynamics to inform precision medicine: a dynamic time warp analysis of 255 depressed inpatients”. In: *BMC Med.* 18.1 (2020), p. 400.

15. Booij MM et al. “Dynamic time warp analysis of individual symptom trajectories in depressed patients treated with electroconvulsive therapy”. In: *J. Affect. Disord.* 293 (2021), pp. 435–443.

16. Sakoe H and Chiba S. “Dynamic programming algorithm optimization for spoken word recognition”. In: *IEEE Trans. Acoust.* 26.1 (1978), pp. 43–49.

17. Fried EI et al. “Mental disorders as networks of problems: a review of recent insights”. In: *Soc. Psychiatry Psychiatr. Epidemiol.* 52.1 (2017), pp. 1–10.

18. Bringmann LF, Lemmens LHJM, Huibers MJH, Borsboom D, and Tuerlinckx F. “Revealing the dynamic network structure of the Beck Depression Inventory-II”. In: *Psychol. Med.* 45.4 (2015), pp. 747–757.

19. Fried EI and Cramer AOJ. “Moving Forward: Challenges and Directions for Psychopathological Network Theory and Methodology”. In: *Perspect. Psychol. Sci.* 12.6 (2017), pp. 999–1020.

20. Cramer AOJ et al. “Major Depression as a Complex Dynamic System”. In: *PLoS One* 11.12 (2016), e0167490.

21. Kasper S and Dienel A. “Cluster analysis of symptoms during antidepressant treatment with Hypericum extract in mildly to moderately depressed out-patients. A meta-analysis of data from three randomized, placebo-controlled trials”. In: *Psychopharmacology* 164.3 (2002), pp. 301–308.

22. Weintraub MJ, Schneck CD, and Miklowitz DJ. “Network analysis of mood symptoms in adolescents with or at high risk for bipolar disorder”. In: *Bipolar Disord.* 22.2 (2020), pp. 128–138.

23. Koenders MA et al. “A Network Approach to Bipolar Symptomatology in Patients with Different Course Types”. In: *PLoS One* 10.10 (2015), e0141420.

24. Rush AJ et al. “The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression”. In: *Biol. Psychiatry* 54.5 (2003), pp. 573–583.

25. Young RC, Biggs JT, Ziegler VE, and Meyer DA. “A rating scale for mania: reliability, validity and sensitivity”. In: *Br. J. Psychiatry* 133 (1978), pp. 429–435.

26. Abdi H, O’Toole AJ, Valentin D, and Edelman B. “DISTATIS: The analysis of multiple distance matrices”. In: *2005 IEEE Computer Society Conference on Computer Vision and Pattern Recognition (CVPR’05)-Workshops.* IEEE. 2005, pp. 42–42.

27. Abdi H, Williams LJ, Valentin D, and Bennani-Dosse M. “STATIS and DISTATIS: optimum multitable principal component analysis and three way metric multidimensional scaling”. In: *Wiley Interdiscip. Rev. Comput. Stat.* 4.2 (2012), pp. 124–167.

28. Kingrani SK, Levene M, and Zhang D. “Estimating the number of clusters using diversity”. In: *Artificial Intelligence Research* 7.1 (2018), pp. 15–22.

29. Lorenzo-Seva U and Berge JMF ten. “Tucker’s Congruence Coefficient as a Meaningful Index of Factor Similarity”. In: *Methodology* 2.2 (2006), pp. 57–64.

30. Briganti G, Kornreich C, and Linkowski P. “A network structure of manic symptoms”. In: *Brain Behav.* 11.3 (2021), e02010.

31. Benazzi F. “Depressive mixed states: unipolar and bipolar II”. In: *Eur. Arch. Psychiatry Clin. Neurosci.* 250.5 (2000), pp. 249–253.

32. Akiskal HS and Benazzi F. *Toward a clinical delineation of dysphoric hypomania - operational and conceptual dilemmas.* 2005.

33. Dilsaver SC, Chen YR, Shoaib AM, and Swann AC. “Phenomenology of mania: evidence for distinct depressed, dysphoric, and euphoric presentations”. In: *Am. J. Psychiatry* 156.3 (1999), pp. 426–430.

34. Sato T, Bottlender R, Kleindienst N, and Möller H.-J. “Syndromes and phenomenological subtypes underlying acute mania: a factor analytic study of 576 manic patients”. In: *Am. J. Psychiatry* 159.6 (2002), pp. 968–974.

35. Malhi GS, Fritz K, Elangovan P, and Irwin L. “Mixed States: Modelling and Management”. In: *CNS Drugs* 33.4 (2019), pp. 301–313.

36. Goldberg JF et al. “Antidepressant use during mixed states: naturalistic outcome data from the STEP-1000”. In: *Neuropsychopharmacology*. Vol. 29. 2004, S144–S144.

37. Koukopoulos A, Albert MJ, Sani G, Koukopoulos AE, and Girardi P. “Mixed depressive states: nosologic and therapeutic issues”. In: *Int. Rev. Psychiatry* 17.1 (2005), pp. 21–37.

38. McNally RJ, Robinaugh DJ, Deckersbach T, Sylvia LG, and Nierenberg AA. “Estimating the symptom structure of bipolar disorder via network analysis: Energy dysregulation as a central symptom”. In: *J. Abnorm. Psychol.* (2021).

39. Madhoo M and Levine SZ. “Network analysis of the Quick Inventory of Depressive Symptomatology: Reanalysis of the STAR* D clinical trial”. In: *Eur. Neuropsychopharmacol.* 26.11 (2016), pp. 1768–1774.

40. Pacchiarotti I et al. “The symptom structure of bipolar acute episodes: in search for the mixing link”. In: *J. Affect. Disord.* 149.1-3 (2013), pp. 56–66.

41. Ng TH et al. “Sleep–wake disturbance in interepisode bipolar disorder and high-risk individuals: A systematic review and meta-analysis”. In: *Sleep Med. Rev.* 20 (2015), pp. 46–58.

42. Solomon DA et al. “Longitudinal course of bipolar I disorder: duration of mood episodes”. In: *Arch. Gen. Psychiatry* 67.4 (2010), pp. 339–347.

43. Hekler EB et al. “Why we need a small data paradigm”. In: *BMC Med.* 17.1 (2019), p. 133.

44. Fisher AJ, Reeves JW, Lawyer G, Medaglia JD, and Rubel JA. *Exploring the idiographic dynamics of mood and anxiety via network analysis*. 2017.

45. Fisher AJ. "Toward a dynamic model of psychological assessment: Implications for personalized care". In: *J. Consult. Clin. Psychol.* 83.4 (2015), pp. 825–836.

CHAPTER 6

Association Between the Fronto-Limbic Network and Cognitive and Emotional Functioning in Individuals With Bipolar Disorder
A Systematic Review and Meta-analysis

Mesbah, R., M. A. Koenders, J. Giltay, N. van der Wee, A. M. van Hemert, M. de Leeuw, 2023. "The fronto-limbic network in relation to cognitive and emotional functioning in bipolar disorder patients: an fMRI meta-analysis." *JAMA Psychiatry, 80 (5), 432-440.* DOI:10.1001/jamapsychiatry.2023.0131

Abstract

Patients with bipolar disorder (BD) suffer from cognitive and emotional dysfunctions. Various brain circuits are implicated in BD but have not been investigated in a meta-analysis of functional Magnetic Resonance Imaging (fMRI) studies. The aim of the current fMRI meta-analysis is to investigate the brain functioning of BD patients compared with healthy controls (HC) in three domains: emotion processing, reward processing, and working memory.

Data were abstracted from articles found through a systematic literature search. The literature search included all the fMRI studies on BD before March 2020. Only fMRI original research studies comparing adult BD patients with HC were included. Studies had to include a task assessing at least one of the domains. i.e., emotion processing, reward processing, or working memory. Differences in brain region activity were tested with whole-brain analysis using the activation likelihood estimation method.

In accordance with PRISMA guidelines, a total of 49 fMRI studies (999 BD, 1027 HC) were included after the selection procedure: 20 studies used an emotion processing task (316 BD, 369 HC), nine studies used a reward processing task (215 BD, 213 HC), and 20 studies used a working memory task (530 BD, 417 HC). As compared to healthy subjects, BD patients showed hyperactivation in the amygdala and hippocampus and hypoactivation in the inferior frontal gyrus during emotion processing, hyperactivation in the orbitofrontal cortex during reward processing, and hyperactivation in the ventromedial prefrontal cortex and subgenual anterior cingulate cortex during working memory activity. Limbic hyperactivation was only found during euthymia in emotion and reward processing domains; abnormalities in frontal cortex activity were also found in BD patients with mania and depression.

This meta-analysis revealed evidence for activity disturbances in key brain areas involved in cognitive and emotion processing in BD patients. Most of the regions are part of the fronto-limbic network. The results suggest that aberrations in the fronto-limbic network, present in both euthymic and symptomatic patients, may be underlying cognitive and emotional dysfunctions in BD.

6.1 Introduction

Bipolar disorder (BD) is a severe psychiatric disorder and is characterized by recurrent depressive and (hypo)manic episodes[1]. These mood fluctuations contribute significantly to functional impairments, including dysfunction in education and work[2]. In addition to affective symptoms, patients with BD show cognitive impairments and emotion regulation deficits during episodes and also during euthymia[3, 4, 5]. As a result, several of these deficits in BD may be considered as a trait-related characteristic of BD. Abnormalities in a variety of brain regions and related circuitry could be underlying cognitive and emotion regulation deficits in BD, with studies in general describing predominantly aberrations in the fronto-limbic network[6, 7, 8, 9], a group of interconnected neural regions including the prefrontal cortex (PFC), amygdala, anterior cingulate cortex (ACC), hippocampus, and nucleus accumbens[10].

BD patients appear to show amygdala hyperactivation during emotion processing across multiple tasks that evoke emotional responses[11]. In addition, recent work shows reduced functional connectivity between the ventrolateral PFC (vlPFC), ACC, orbitofrontal cortex (OFC), and limbic areas, which points towards a more complex aberrant interplay between frontal and limbic structures, instead of amygdala hyperactivity alone[10]. In addition to emotion, BD patients show increased activity in fronto-limbic regions during reward processing, amongst others in the PFC, ACC, and striatum[12, 13, 14]. Studies of working memory in BD have reported deviant frontal cortex activity[15, 16, 17], including medial frontal gyri hyperactivation[18] and dorsolateral PFC (dlPFC) hypoactivation[19, 20, 21].

Across all emotional and cognitive domains, inconsistent findings have been found, and as a result a robust hypothesis on fronto-limbic dysfunction in BD is lacking[22]. Not surprisingly, and probably related to aberrant brain activity, BD patients showed behavioral deficiencies in terms of decreased task performance during emotion and reward processing, as well as during cognitive tasks that demand working memory activity[4, 23, 24, 25, 26]. In addition to decreased task performances, fronto-limbic network deficiencies may also be involved in aberrant psychological mechanisms in BD such as state-independent emotional hyper-reactivity, rumination and the intense pursuit of goals and focus on achievement[27, 28, 29].

Cognitive and emotion tasks that involve fronto-limbic brain activity have been intensively studied. Emotion processing involves attentional processes towards (emotional) stimuli, their interpretation, and the regulation of activated emotions (the ability to monitor and modify the occurrence, intensity, and duration of an ongoing response to emotional stimuli)[30]. Activations in subcortical regions are strongly associated with modulating and generating emotions, whereas frontal regions are involved in the evolution and regulation of emotional responses[10, 26]. The three primary functions of reward processing include associative learning (classical conditioning and operant reinforcement), incentive salience (motivation and desire), and positively-valenced emotions (pleasure and hedonic)[31]. In particular, pleasure coding reward has been described to be associated with activation in the OFC[32], whereas ACC activity is related to reward anticipation[33]. In addition to the ACC, the ventral striatum has a key function in anticipation of reward stimuli and is part of a complex circuit involving limbic regions such as the amygdala, attributing feelings towards the experienced reward[34]. Working memory is seen as a platform where information temporarily can be held, manipulated, and then used to adjust goal-directed behavior[35, 36]. Studies of working memory have pointed to the involvement of the dlPFC, dorsal and anterior ACC, and parietal cortex[37]. The dlPFC is associated with the integration and retrieval of information that is stored or taxing load[38]. The ACC is implicated in evaluative processes to adjust and adapt the received information depending on demand[39]. In addition to fronto-limbic regions, the parietal cortex seems to be a workspace for processing sensory and perceptual information[40, 41, 42]. In sum, tasks associated with emotion processing, reward processing, and working memory are all dependent on an adequate activation of fronto-limbic brain regions and can therefore be used to assess functioning in this network.

Although there is an increasing number of fMRI studies suggesting fronto-limbic functional abnormalities in BD, a meta-analysis specifically focusing on this brain network in BD has not yet been performed. A meta-analysis of fronto-limbic network activity in BD is important as malfunctioning of this brain network can be considered as reflecting part of the pathophysiology of cognitive and emotional impairments in BD. Therefore, in the current study, we conducted a meta-analysis of fMRI studies in patients with BD investigating emotion processing, reward processing, or working memory, domains which all rely on proper fronto-limbic network activity. By performing this meta-analysis, we aim to aggregate the evidence to be able to draw more rigorous conclusions regarding the potential abnormalities in the fronto-limbic network in BD. Moreover, we want to elucidate if trait (i.e., euthymia) or state (i.e., mania or depression) affects potential fronto-limbic network alterations.

6.2 Methods

6.2.1 Literature search and selection

For the selection procedure PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[43, 44] guidelines were followed (see eTable 6.3 in Appendix). The PRISMA flow chart depicting the process for the systematic literature search and selection of the studies is shown in eFigure 6.4 (Appendix). The literature search was conducted in the databases of PubMed, Embase, Web of Science, COCHRANE Library, PsycINFO, Emcare, Academic Search Premier, and ScienceDirect. The following keywords were used in the literature search: bipolar disorder, manic depression, functional magnetic resonance imaging (fMRI), mania, and bipolar depression (see appendix for the extensive literature search). Articles were eligible if written in English and with subjects between 18 and 65 years old. All healthy controls (HC) were physically and neurologically healthy, with no current psychopathology. Exclusion criteria for all participants were medical or neurological illnesses that might influence brain function, and any contraindications for receiving an MRI scan. Literature reviews, meta-analyses, methodological articles, case reports, letters, conference abstracts, and editorials were excluded. Selection of literature was conducted using three main inclusion criteria: 1) task-related fMRI studies on BD with whole-brain analyses, 2) studies had to include a task assessing at least one of the domains. i.e. emotion processing, reward processing, or working memory, 3) studies compared adult patients with BD with HC. Exclusion criteria were: fMRI studies using a region-of-interest (ROI) analysis approach, only assessing functional connectivity, and resting-state studies. Additionally, studies including only subjects with high-risk for BD, BD relatives, BD offspring, or childhood BD (<18 years) were excluded. Finally, the studies were grouped into at least one of the three domains.

For each study, data were extracted (i.e. first author, year of publication, mean age, gender, number of BD patients and HC, mood state, contrasts, details about tasks, imaging results as coordinated clusters [X,Y,Z] in voxels and details of the fMRI paradigm), which were used for description and further analyses. The fMRI studies were allocated to three task domains (i.e., emotion processing, reward processing, and working memory). Two fMRI studies examined two different domains and were therefore included in two different analyses[13, 45].

6.2.2 Statistical analysis

Meta-analyses were conducted using the software GingerALE version 3.0.2[43, 44]. Differences in brain activation among regions associated with each domain were analyzed separately using the activation likelihood estimation (ALE) method. The ALE approach uses modeling of activation locations (foci) by a 3D Gaussian, calculating the overlap of the distributions across experiments using the spatial uncertainty of the foci[44]. It forms a probabilistic map of the likelihood that each voxel was activated by an experiment.

The analyses for each domain involved two analyses of contrasts. First, we analyzed the activation in brain areas that were more active in BD brains compared to HC, indicating hyperactivation in BD. Second, we analyzed the activation in brain areas which were more active in HC brains compared to BD, referring to hypoactivation in BD. The voxel-level Family-Wise Error (FWE) method ($p = 0.05$) was used for the correction of all the analyses and contrasts of different domains. The number of threshold permutations was set at 1000, and the p-value threshold at 0.05 with a minimum cluster size of suprathreshold voxels exceeding 100 mm^3. Next, we performed sensitivity analyses focused on mood states. For each domain, we analyzed the effect of mood states separately (euthymic, manic, and depressive). For these analyses, a similar procedure was followed.

6.3 Results

In total, 49 whole-brain-based fMRI studies were included, which accrued 999 BD patients and 1027 HC. The included studies (per domain) and their clinical specifications are listed in eTable 6.3 (Appendix). All meta-analytical results are presented in Table 6.1 and 6.2.

6.3.1 Emotion processing

For emotion processing, a total of 20 studies were included, with in total 324 patients with BD and 369 HC. Patients with BD had different mood states; 116 (35.8%) were euthymic, 70 (21.4%), depressed, 44 (13.6%) were (hypo)manic, one mixed state (0.3%), and the rest were not specified (n = 93, 28,7%). The emotion processing domain included emotion tasks with a variety of paradigms including emotionally salient stimuli (i.e., affect induction, emotional perception of facial emotions or prosody, emotion regulation, emotion recognition, emotion memory, or inhibition tasks.

Hyperactivation was shown in all BD patients compared with HC (Table 6.1) in a part of the left hippocampus, the left and right anterior temporal cortex, and the left amygdala (Figure 6.1A). Hypoactivation in BD patients was found only in the right inferior frontal gyrus (IFG) as compared to HC (Figure 6.1B).

The results regarding mood states (Table 6.2) revealed hyperactivation in the left parahippocampal gyrus and hypoactivation in the left IFG in BD patients who were in the euthymic state. During mania, we found hyperactivation in the left thalamus and hypoactivation in right IFG in patients with BD.

6.3.2 Reward processing

A total of nine studies on reward processing were included, with in total 195 BD patients and 213 HC. 117 (60%) of BD patients were euthymic, 65 (33.3%) depressed, 10 (5.1%) were (hypo)manic and three were in a mixed state (1.5%). The reward processing domain paradigms included monetary incentive, gambling, card number guessing, and Roulette tasks.
Taking all BD patients together (Table 6.1), only hyperactivation in the left OFC was shown as compared to HC (Figure 6.2).

For euthymic mood state in BD patients, hyperactivation was found in the left parahippocampal gyrus, ACC, MFG, and right temporal gyrus compared to HC. Patients who were in a depressive mood state showed hyperactivation in the left IFG and in the right superior temporal gyrus (see Table 6.2). A meta-analysis in manic BD patients could not be performed due to a lack of power.

6.3.3 Working memory

We included 20 studies with 530 BD patients and 417 HC for working memory. There were 178 (36.1%) patients in euthymic state, 171 (34.7%) depressed patients, 124 (25.1%)

(hypo)manic, and 57 (10.8%) were not specified. The majority of the studies used a letter n-back task and a few studies a delayed match to sample task.

Overall, hyperactivation in BD patients was found in the subgenual ACC (sgACC) and ventromedial PFC (vmPFC) (Figure 6.3) as compared to HC (Table 6.1).

With regard to mood states, no difference in euthymic BD patients were found compared to HC. Patients who were (hypo)manic showed hyperactivity in left ACC and hypoactivation in left IFG during working memory. Depressed BD patients showed hyperactivation in the left PFC and ACC; hypoactivation was found in the right partial lobe and left cerebellum (see Table 6.2).

	Peak coordinates						
Anatomical label	x	y	z	BA	Z	Cluster size (mm^3)	ALE Value
Emotion processing							
Bipolar disorder → Healthy controls							
left Hippocampus	-18	-14	-10	28	6.70	864	0.0293
right Superior temporal gyrus	48	14	-10	38	6.06	176	0.0251
left Superior temporal gyrus	-56	-16	6	41	5.86	176	0.0251
left Amygdala	-28	-2	-12	-	5.52	160	0.0217
Healthy controls → Bipolar disorder							
right Inferior frontal gyrus	42	22	0	47	6.38	232	0.0241
Reward processing							
Bipolar disorder → Healthy controls							
left Orbitofrontal cortex	-46	30	0	47	6.22	344	0.0240
Working memory							
Bipolar disorder → Healthy controls							
left Subgenual anterior cingulate	-6	34	-10	32	6.82	696	0.0323
left Ventromedial prefrontal cortex	-2	46	-10	10	6.63	624	0.0308

Table 6.1: Activation likelihood estimation meta-analytical results of whole brain-based studies. Talairach coordinates are reported. BA = Brodmann area. The voxel-level Family-Wise Error (FWE) method ($p = 0.05$) was used for the correction of all the analyses and contrasts of different domains. The number of threshold permutations was set at 1000, and the p-value threshold at 0.05 with a minimum cluster size of suprathreshold voxels exceeding 100 mm 3.

Table 6.2: Activation likelihood estimation meta-analytical results of whole brain-based studies per mood state. Talairach coordinates are reported. BA = Brodmann area. The voxel-level Family-Wise Error (FWE) method (p = 0.05) was used for the correction of all the analyses and contrasts of different domains. The number of threshold permutations was set at 1000, and the p-value threshold at 0.05 with a minimum cluster size of suprathreshold voxels exceeding 100 mm 3.

N.S. = Not Significant, N.A. = Not Applicable due to limited power.

	Peak coordinates						
Anatomical label	x	y	z	BA	Z	Cluster size (mm^3)	ALE Value
Emotion processing							
Euthymia							
Bipolar disorder → Healthy controls							
left Parahippocampal gyrus	-24	-20	-10	28	5.62	216	0.0191
Healthy controls → Bipolar disorder							
left Inferior frontal gyrus	-56	10	26	9	5.28	168	0.0141
Mania							
Bipolar disorder → Healthy controls							
left Thalamus	-4	-32	10	-	5.91	312	0.0176
Healthy controls → Bipolar disorder							
right Inferior frontal gyrus	46	26	-2	47	5.31	224	0.0141
Depression							
Bipolar disorder → Healthy controls							
left Angular gyrus (Parietal Lobe)	-32	-56	32	39	5.63	104	0.0183
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.S.
Reward processing							
Euthymia							
Bipolar disorder → Healthy controls							
left Parahippocampal gyrus	-22	-42	-10	36	5.81	152	0.0188
left Anterior cingulate	-16	42	0	32	5.81	152	0.0188
left Medial frontal gyrus	-16	48	-6	10	5.81	152	0.0188
right Middle temporal gyrus	60	-4	-8	21	5.81	152	0.0188
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.A.

Continued on next page

Table 6.2 – continued from previous page

Anatomical label	Peak coordinates x	y	z	BA	Z	Cluster size (mm^3)	ALE Value
Depression							
Bipolar disorder → Healthy controls							
left Inferior frontal gyrus	-48	28	-1	47	5.46	100	0.0170
right Superior temporal gyrus	48	-22	-2	22	5.65	100	0.0175
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.S.
Mania							
Bipolar disorder → Healthy controls	-	-	-	-	-	-	N.A.
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.A.
Working memory							
Euthymia							
Bipolar disorder → Healthy controls	-	-	-	-	-	-	N.S.
Healthy controls → Bipolar disorder	-	-	-	-	-	-	N.S.
Mania							
Bipolar disorder → Healthy controls							
left Anterior cingulate	-6	40	4	32	6.26	400	0.0224
Healthy controls → Bipolar disorder							
left Middle frontal gyrus	-30	-6	56	6	8.30	624	0.0367
Depression							
Bipolar disorder → Healthy controls							
left Prefrontal cortex	-2	46	-10	10	7.18	504	0.0277
left Anterior cingulate	-4	36	-4	32	5.76	112	0.0189
Healthy controls → Bipolar disorder							
right Parietal lobe	8	-66	56	7	5.70	112	0.0184
left Cerebellum	-30	-52	-32	-	5.71	104	0.0185

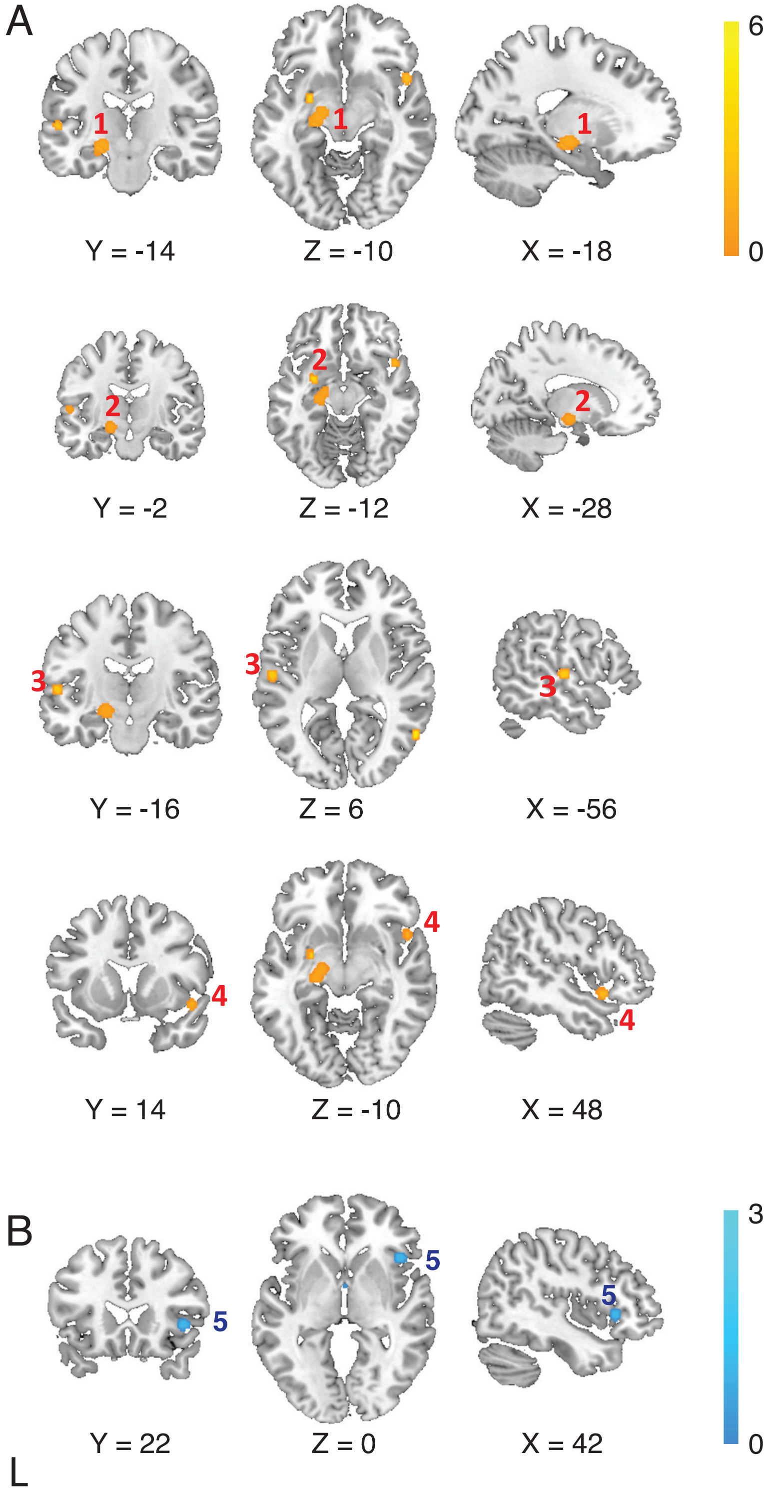

A
6
0
1
Y = -14
Z = -10
X = -18
2
Y = -2
Z = -12
X = -28
3
Y = -16
Z = 6
X = -56
4
Y = 14
Z = -10
X = 48
B
3
0
5
Y = 22
Z = 0
X = 42
L

Figure 6.1: Meta-analytic maps of brain functional changes of domain emotional processing : significant brain hyperactivation (A) in 1. left hippocampus, 2. left amygdala, 3. left anterior temporal cortex and 4. right anterior temporal cortex. Significant brain hypoactivation (B) in 5. right IFG. The right side of all coronal and axial images corresponds to the right side of the brain. Colorbars represent z-values.

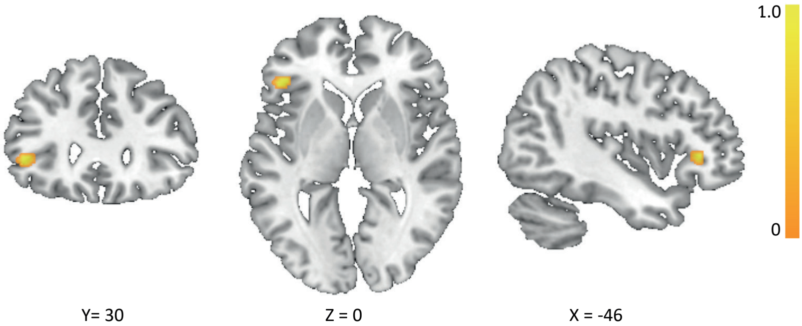


Figure 6.2: Meta-analytic maps of brain functional changes of domain reward processing: significant brain hyperactivation in left OFC. The right side of all coronal and axial images corresponds to the right side of the brain. Colorbar represents z-values.

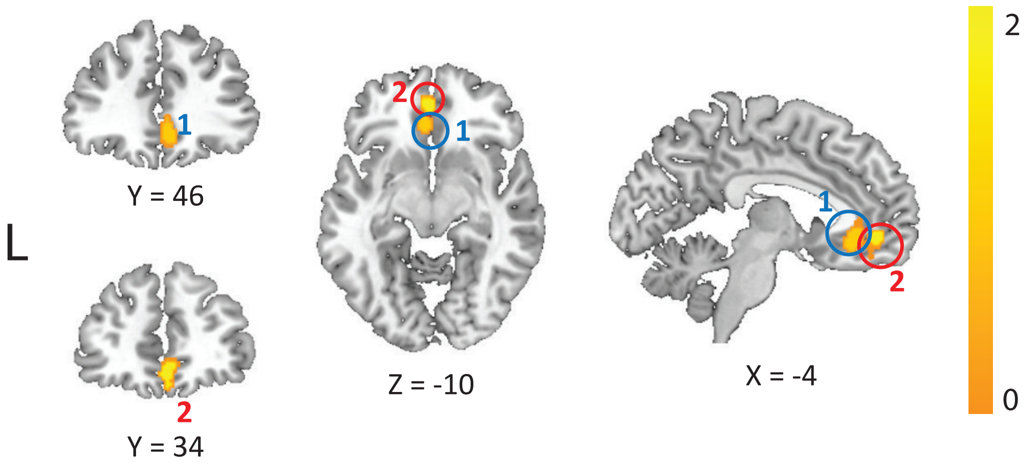


Figure 6.3: Meta-analytic maps of brain functional changes of domain working memory : significant brain hyperactivation in left 1. subgenual anterior cingulate and 2. ventromedial PFC. The right side of all coronal and axial images corresponds to the right side of the brain. Colorbar represents z-values.

6.4 Discussion

In the current meta-analysis, we investigated brain functioning in patients with BD as compared to HC within cognitive domains related to emotion processing, working memory, and reward processing. Our findings revealed significant differences in brain activity in BD patients mostly within the fronto-limbic network. Specifically, limbic activation alterations were only manifested in euthymic BD patients, whereas more widespread frontal dysfunctions were also found during depression and mania. As such, one can assume that aberrant limbic activity during cognitive and emotion processing may be a trait-related BD characteristic, on the other hand, disruptions in frontal cortex activity may be associated with state-related factors.

During emotion processing, we found that patients with BD showed hyperactivation in the hippocampus, parts of the temporal cortex, and amygdala, and hypoactivation in the right IFG (as part of the PFC) when all affective states are pooled together. This is in line with an earlier meta-analysis[7] and a systematic review[11] that focused on emotion processing and found abnormal activity in the fronto-limbic network. Our results regarding the emotion processing domain can be functionally interpreted. For instance, amygdala hyperactivation may be interpreted as reflecting a state of 'oversensitivity', resulting in increased amygdala responses even when there is no need to. The amygdala has a crucial role in emotion generation (i.e. perception and arousal), identification of emotional stimuli[46, 47, 48], and emotion regulation[49]. In addition to amygdala hyperactivation during emotion processing, we also found increased activation in the hippocampus. Besides its crucial role in memory, this region is also involved in socio-emotional processing and the production of affective states[48, 50]. Further, hyperactivation was found in the temporal cortex, which is notably involved in social and emotion processing, recognition, and semantic memory[51]. Our results regarding emotion processing also encompassed hypoactivation in the IFG, which is known to be associated with inhibitory control[52]. Inhibition is a major subcomponent of executive function and is defined as the ability to suppress the process of irrelevant stimuli and dominant response when inappropriate[53]. The inability to inhibit responses is, among others, associated with impulsive behavior[54]. Moreover, BD patients might have difficulties in the identification of emotional stimuli (either negative or positive) leading to increased arousal, making it more difficult to regulate their emotions and this, in turn, may provoke mood episodes states[55]. From a network perspective, hypoactivity in inhibitory structures such as the IFG might be related to hyperactivity in the whole network related to fronto-limbic system (as found here; hippocampus, parts of the temporal cortex, and amygdala) that normally should be inhibited[56].

For reward processing, our results showed hyperactivation in the left OFC in BD. OFC activity is important for pleasure coding as well as reward outcome and for processing the experience of hyperhedonia[32]. This region forms the key in a hypersensitivity model of reward processing that was introduced based on a behavioral approach system (BAS) hypothesis for BD[57]. The concept of BAS refers to the hypothesis that bipolar patients have a hypersensitive reward system that leads to overreaction or underreaction to reward-related cues. It states that excessive reward system activation leads to (hypo)manic symptoms, whereas excessive deactivation gives rise to depressive symptoms[57]. This model is thought to be associated with hyperdopaminergia which leads to high-risk, high-reward seeking behavior observed during mania[58]. Our finding of OFC hyperactivation in BD is in line with this reward hypersensitivity model of BD.

To our best knowledge, no previous meta-analyses of neuroimaging studies have focused on the reward system in bipolar patients. To date, only a systematic review on imaging findings during reward processing in unaffected first-degree relatives has been performed[59]. Although relatives are non-affected and do not have symptoms, these genetically at-risk subjects seem to show reward-related activity dysfunction similar to BD patients, i.e. increased OFC in response to reward[59]. The fact that the current meta-analysis in a large sample of BD patients found a similar OFC activity pattern as found in healthy relatives, underlines the importance of these aberrations as they may serve as an important element in the pathological pathway towards BD.

For working memory tasks, our results showed hyperactivation in the sgACC and vmPFC as compared to HC. Interestingly, these regions are connected to limbic structures and are functionally involved in reward valuation and emotion regulation, but recent studies highlight the role in working memory as well. Both sgACC and vmPFC play an important role in integrating cognitive and emotional stimuli. For example, the vmPFC structurally connects the amygdala with the dlPFC and functionally regulates the influencing effects of capacity-exceeding working memory load from the dlPFC and the mediating deleterious effects of emotional interference on cognitive processing in the amygdala[60, 61]. In addition, the sgACC is seen as another bridge between the dlPFC and amygdala, and plays a role in emotional processing and attention[62]. The interconnection of these two regions to the dlPFC and the amygdala facilitates interactions between emotion and cognition[61]. Our results provide further support for the potential role of dysregulated vmPFC and sgACC activity as a direct contributor to poor working memory performance and deficiencies in emotional processing in BD.

In addition to the whole BD group, analyses were also performed per mood state. Limbic hyperactivity was only found in euthymic BD patients (parahippocampal), whereas abnormalities in frontal activation, although with a more widespread pattern, were also revealed during states of depression and mania. A tentative conclusion can be drawn that limbic hyperactivation during emotion and cognitive processing in BD may be a trait-dependant characteristic, whereas frontal cortex dysfunction may also be affected during states in BD. Functionally, failed frontal inhibitory control may be more pronounced when patients suffer from a depressive or manic episode, while the earlier mentioned increased limbic 'oversensitivity' may only occur during euthymia and may potentially be a risk factor for provoking mood states[55]. Given power constraints, these conclusions should be interpreted with caution. It can therefore not be ruled out that increased limbic activity could also be the case during mania or depression, however, the current meta-analysis shows that frontal hypoactivation may be a more robust state-dependent finding. One could hypothesize that during affective states BD patients take high-dose or other medication as compared to euthymia, which may potentially normalize limbic activity[63].

Two earlier meta-analyses with smaller numbers of inclusions investigated task fMRI studies in BD[7, 64]. Our findings regarding emotional processing are consistent with limbic hyperactivation and IFG hypoactivation as found in one meta-analysis[7]. However, all kinds of paradigms related to a variety of cognitive functions were included, while the current meta-analysis focused on working memory, emotional and reward processing with regard to the hypothesis of impaired fronto-limbic network activity in BD specifically. One other meta-analysis focused on the comparison between BD youth and adults[64]. Interestingly, similar amygdala hyperactivation during emotional tasks and pgACC hyperactivation during non-emotional tasks was found in BD youth, which underlines the important role of these brain areas in the psychopathology of BD and suggest common trait-like abnormalities.

To the best of our knowledge, this is the first meta-analysis showing robust fronto-limbic network abnormalities during emotion and cognitive functioning. The differentiation of three cognitive domains in relation to fronto-limbic network functioning in BD allowed a better perspective on how neurocognitive abnormalities can co-exist in parallel.

Some limitations need to be noted. First, although significant results were revealed in the analyses per mood state, the number of BD subjects for the different states was limited. As mentioned above, this may result in the negative finding of unincreased limbic activity during affective states. Future studies specifically focusing on state-related emotional and cognitive functioning are required to increase the power of meta-analyses. Second, we were unable to perform sensitivity analyses and disentangle the potential effects of psychopharmaceuticals due to heterogeneity in medication[65]. The great majority of patients was treated with a mood-stabilizer as monotherapy or in combination with other psychotropics. However, a review in BD patients found no significant medication effects on brain activation[66]. Third, clinical heterogeneity and demographic features often make it complicated to compare across studies. To obtain generalizable results, we included a broad range of studies, conditions, and multiple contrasts in three domains of interest, although cognitively impaired subjects were excluded. Meta-analytic results help one to draw overriding conclusions and identify consistency in the literature despite heterogeneity, while they might lack specificity as to the nature of any aberration. A final limitation is that we could not correct for specific participant factors, including symptomatology such as psychosis. A few studies measured and reported psychotic symptoms, while others did not mention anything. In addition, because of the lack of information, we also did not model gender, medication and comorbidity, factors that might have effects on brain activity in patients with BD. However, it is known that in particular mood states are strongly associated with confounding fMRI results, specifically the fronto-limbic network[67]. In the current analyses, we were able to tackle this important factor.

The current study is the first meta-analysis in BD patients investigating brain activity during cognitive and emotional tasks that demand proper fronto-limbic functioning. We were able to demonstrate that the fronto-limibic network is thoroughly affected in BD, both in euthymic as well as symptomatic patients. Regarding reward processing specifically, more studies are needed to replicate and expand our findings. Moreover, fMRI studies in BD would benefit from the standardization of reward paradigms. Finally, the field will be furthered by using novel approaches such as multimodal analyses and pattern-recognition techniques. These advances will likely increase the clinical and scientific relevance of reward processing fMRI paradigms in BD, which may result in their use during diagnostics or in investigating therapeutic targets. Longitudinal fMRI studies following at-risk patients as well as first-onset BD patients are needed to examine the development of cognitive impairments and its association with fronto-limbic findings over the course of BD.

Bibliography

1. Judd LL et al. “The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders?” In: *J. Affect. Disord.* 73.1-2 (2003), pp. 19–32.
2. Grande I, Berk M, Birmaher B, and Vieta E. *Bipolar disorder*. 2016.
3. Martinez-Aran A et al. “Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome”. In: *Bipolar Disord.* 6.3 (2004), pp. 224–232.
4. Bora E, Yucel M, and Pantelis C. “Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives”. In: *J. Affect. Disord.* 113.1-2 (2009), pp. 1–20.
5. Robinson LJ et al. “A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder”. In: *J. Affect. Disord.* 93.1-3 (2006), pp. 105–115.
6. Kohn N et al. “Neural network of cognitive emotion regulation–an ALE meta-analysis and MACM analysis”. In: *Neuroimage* 87 (2014), pp. 345–355.
7. Chen C.-H, Suckling J, Lennox BR, Ooi C, and Bullmore ET. “A quantitative meta-analysis of fMRI studies in bipolar disorder”. In: *Bipolar Disord.* 13.1 (2011), pp. 1–15.
8. Strakowski SM et al. “Abnormal FMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task”. In: *Am. J. Psychiatry* 162.9 (2005), pp. 1697–1705.
9. Strakowski SM, Delbello MP, and Adler CM. “The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings”. In: *Mol. Psychiatry* 10.1 (2005), pp. 105–116.
10. Bi B, Che D, and Bai Y. “Neural network of bipolar disorder: Toward integration of neuroimaging and neurocircuit-based treatment strategies”. In: *Transl. Psychiatry* 12.1 (2022), p. 143.
11. Townsend J and Altshuler LL. “Emotion processing and regulation in bipolar disorder: a review”. In: *Bipolar Disord.* 14.4 (2012), pp. 326–339.

12. Chase HW et al. “Dissociable patterns of abnormal frontal cortical activation during anticipation of an uncertain reward or loss in bipolar versus major depression”. In: *Bipolar Disord.* 15.8 (2013), pp. 839–854.

13. Jogia J, Dima D, Kumari V, and Frangou S. “Frontopolar cortical inefficiency may underpin reward and working memory dysfunction in bipolar disorder”. In: *World J. Biol. Psychiatry* 13.8 (2012), pp. 605–615.

14. Nusslock R et al. “Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults”. In: *Bipolar Disord.* 14.3 (2012), pp. 249–260.

15. Adler CM, Holland SK, Schmithorst V, Tuchfarber MJ, and Strakowski SM. “Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task”. In: *Bipolar Disord.* 6.6 (2004), pp. 540–549.

16. Drapier D et al. “Genetic liability for bipolar disorder is characterized by excess frontal activation in response to a working memory task”. In: *Biol. Psychiatry* 64.6 (2008), pp. 513–520.

17. Thermenos HW et al. “An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder”. In: *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 153B.1 (2010), pp. 120–131.

18. Monks PJ et al. *A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction.* 2004.

19. Townsend J, Bookheimer SY, Foland-Ross LC, Sugar CA, and Altshuler LL. “fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects”. In: *Psychiatry Res.* 182.1 (2010), pp. 22–29.

20. Hamilton LS et al. “Alterations in functional activation in euthymic bipolar disorder and schizophrenia during a working memory task”. In: *Hum. Brain Mapp.* 30.12 (2009), pp. 3958–3969.

21. Frangou S, Kington J, Raymont V, and Shergill SS. “Examining ventral and dorsal prefrontal function in bipolar disorder: a functional magnetic resonance imaging study”. In: *Eur. Psychiatry* 23.4 (2008), pp. 300–308.

22. Townsend JD et al. “Frontal-amygdala connectivity alterations during emotion downregulation in bipolar I disorder”. In: *Biol. Psychiatry* 73.2 (2013), pp. 127–135.

23. Krabbendam L, Arts B, Os J van, and Aleman A. “Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review”. In: *Schizophr. Res.* 80.2-3 (2005), pp. 137–149.

24. Arts B, Jabben N, Krabbendam L, and Os J van. *Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives.* 2008.

25. Koenders MA et al. “Understanding bipolar disorder within a biopsychosocial emotion dysregulation framework”. In: *Journal of Affective Disorders Reports* 2 (2020), p. 100031.

26. Dickstein DP et al. “Altered neural function in pediatric bipolar disorder during reversal learning”. In: *Bipolar Disord.* 12.7 (2010), pp. 707–719.

27. Fuhr K, Hautzinger M, and Meyer TD. “Implicit motives and cognitive variables: specific links to vulnerability for unipolar or bipolar disorder”. In: *Psychiatry Res.* 215.1 (2014), pp. 61–68.
28. Johnson SL and Carver CS. “Extreme Goal Setting and Vulnerability to Mania Among Undiagnosed Young Adults”. In: *Cognit. Ther. Res.* 30.3 (2006), pp. 377–395.
29. Nusslock R, Young CB, and Damme KSF. “Elevated reward-related neural activation as a unique biological marker of bipolar disorder: assessment and treatment implications”. In: *Behav. Res. Ther.* 62 (2014), pp. 74–87.
30. Morawetz C, Bode S, Derntl B, and Heekeren HR. “The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies”. In: *Neurosci. Biobehav. Rev.* 72 (2017), pp. 111–128.
31. Schultz W. “Neuronal Reward and Decision Signals: From Theories to Data”. In: *Physiol. Rev.* 95.3 (2015), pp. 853–951.
32. Berridge KC and Kringelbach ML. “Pleasure systems in the brain”. In: *Neuron* 86.3 (2015), pp. 646–664.
33. Liu X, Hairston J, Schrier M, and Fan J. “Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies”. In: *Neurosci. Biobehav. Rev.* 35.5 (2011), pp. 1219–1236.
34. Haber SN and Knutson B. “The reward circuit: linking primate anatomy and human imaging”. In: *Neuropsychopharmacology* 35.1 (2010), pp. 4–26.
35. Chatham CH and Badre D. “Multiple gates on working memory”. In: *Curr Opin Behav Sci* 1 (2015), pp. 23–31.
36. Vogel EK and Machizawa MG. “Neural activity predicts individual differences in visual working memory capacity”. In: *Nature* 428.6984 (2004), pp. 748–751.
37. Dima D, Jogia J, and Frangou S. *Dynamic causal modeling of load-dependent modulation of effective connectivity within the verbal working memory network*. 2014.
38. Chai WJ, Abd Hamid AI, and Abdullah JM. “Working Memory From the Psychological and Neurosciences Perspectives: A Review”. In: *Front. Psychol.* 9 (2018), p. 401.
39. Osaka M et al. “The neural basis of individual differences in working memory capacity: an fMRI study”. In: *Neuroimage* 18.3 (2003), pp. 789–797.
40. Braver TS and Bongiolatti SR. “The role of frontopolar cortex in subgoal processing during working memory”. In: *Neuroimage* 15.3 (2002), pp. 523–536.
41. Rodriguez Merzagora AC, Izzetoglu M, Onaral B, and Schultheis MT. “Verbal working memory impairments following traumatic brain injury: an fNIRS investigation”. In: *Brain Imaging Behav.* 8.3 (2014), pp. 446–459.
42. Andersen RA and Cui H. “Intention, action planning, and decision making in parietal-frontal circuits”. In: *Neuron* 63.5 (2009), pp. 568–583.
43. Eickhoff SB, Bzdok D, Laird AR, Kurth F, and Fox PT. “Activation likelihood estimation meta-analysis revisited”. In: *Neuroimage* 59.3 (2012), pp. 2349–2361.
44. Eickhoff SB et al. *Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty*. 2009.

45. Moser DA et al. “Multivariate Associations Among Behavioral, Clinical, and Multimodal Imaging Phenotypes in Patients With Psychosis”. In: *JAMA Psychiatry* 75.4 (2018), pp. 386–395.

46. Anderson AK. “Feeling emotional: the amygdala links emotional perception and experience”. In: *Soc. Cogn. Affect. Neurosci.* 2.2 (2007), pp. 71–72.

47. Bradley MM et al. “Activation of the visual cortex in motivated attention”. In: *Behav. Neurosci.* 117.2 (2003), pp. 369–380.

48. Phillips ML, Drevets WC, Rauch SL, and Lane R. “Neurobiology of emotion perception I: The neural basis of normal emotion perception”. In: *Biol. Psychiatry* 54.5 (2003), pp. 504–514.

49. Banks SJ, Eddy KT, Angstadt M, Nathan PJ, and Phan KL. “Amygdala–frontal connectivity during emotion regulation”. In: *Soc. Cogn. Affect. Neurosci.* 2.4 (2007), pp. 303–312.

50. Amunts K et al. “Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps”. In: *Anat. Embryol.* 210.5-6 (2005), pp. 343–352.

51. Ding S.-L, Van Hoesen GW, Cassell MD, and Poremba A. “Parcellation of human temporal polar cortex: a combined analysis of multiple cytoarchitectonic, chemoarchitectonic, and pathological markers”. In: *J. Comp. Neurol.* 514.6 (2009), pp. 595–623.

52. Green MJ, Cahill CM, and Malhi GS. “The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder”. In: *J. Affect. Disord.* 103.1-3 (2007), pp. 29–42.

53. Logan GD and Cowan WB. “On the ability to inhibit thought and action: A theory of an act of control”. In: *Psychol. Rev.* 91.3 (1984), p. 295.

54. Morsel AM et al. *Inhibitory control in euthymic bipolar disorder: Event related potentials during a Go/NoGo task.* 2017.

55. García-Blanco AC, Perea M, and Salmerón L. “Attention orienting and inhibitory control across the different mood states in bipolar disorder: an emotional antisaccade task”. In: *Biol. Psychol.* 94.3 (2013), pp. 556–561.

56. Zhang L et al. “Aberrant brain network topology in the frontoparietal-limbic circuit in bipolar disorder: a graph-theory study”. In: *Eur. Arch. Psychiatry Clin. Neurosci.* 271.7 (2021), pp. 1379–1391.

57. Alloy LB, Olino T, Freed RD, and Nusslock R. “Role of Reward Sensitivity and Processing in Major Depressive and Bipolar Spectrum Disorders”. In: *Behav. Ther.* 47.5 (2016), pp. 600–621.

58. Burdick KE, Braga RJ, Gopin CB, and Malhotra AK. “Dopaminergic influences on emotional decision making in euthymic bipolar patients”. In: *Neuropsychopharmacology* 39.2 (2014), pp. 274–282.

59. Miskowiak KW et al. *The search for neuroimaging and cognitive endophenotypes: A critical systematic review of studies involving unaffected first-degree relatives of individuals with bipolar disorder.* 2017.

60. Zhang L et al. “Distinct temporal brain dynamics in bipolar disorder and schizophrenia during emotion regulation”. In: *Psychol. Med.* 50.3 (2020), pp. 413–421.

61. Farruggia MC, Laird AR, and Mattfeld AT. “Common default mode network dysfunction across psychopathologies: a neuroimaging meta-analysis of the n-back working memory paradigm”. In: *bioRxiv* (2020), pp. 2020–.

62. Zhang F.-F, Peng W, Sweeney JA, Jia Z.-Y, and Gong Q.-Y. “Brain structure alterations in depression: Psychoradiological evidence”. In: *CNS Neurosci. Ther.* 24.11 (2018), pp. 994–1003.

63. Müller-Oerlinghausen B, Berghöfer A, and Bauer M. “Bipolar disorder”. In: *Lancet* 359.9302 (2002), pp. 241–247.

64. Wegbreit E et al. *Developmental Meta-analyses of the Functional Neural Correlates of Bipolar Disorder*. 2014.

65. Phillips ML and Swartz HA. “A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research”. In: *Am. J. Psychiatry* 171.8 (2014), pp. 829–843.

66. Phillips ML, Travis MJ, Fagiolini A, and Kupfer DJ. “Medication effects in neuroimaging studies of bipolar disorder”. In: *Am. J. Psychiatry* 165.3 (2008), pp. 313–320.

67. Norwood MF et al. “Brain activity, underlying mood and the environment: A systematic review”. In: *J. Environ. Psychol.* 65 (2019), p. 101321.

6.5 Supplementary Online Content

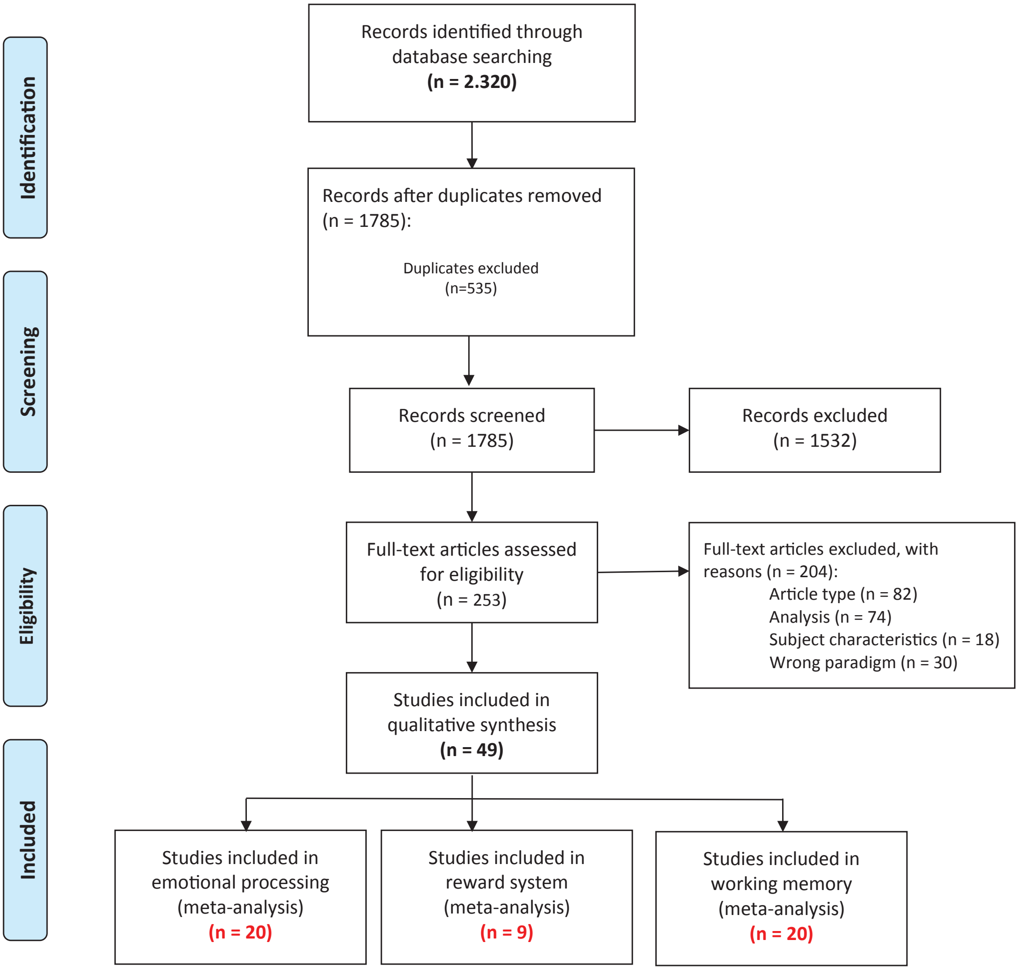
eMethods. Literature search

The literature search included all the fMRI studies on BD before March 2020. An independent employee of the Walaeus Library (Leiden University Libraries) performed the literature search. The auteurs screened first for eligibility based on titles and abstracts according to the inclusion and exclusion criteria. When this was unclear, the full-text review was carried out. The full-text of the remaining studies was beside the auteurs reviewed independently by two interns in the field of psychology. Disagreements were managed by discussion to reach a consensus.

We used the following key words (using both free-text and MeSH search):

(("fMRI"[tw] OR "f mri"[tw] OR fmr imag*[tw] OR functional magnetic*[tw] OR "functional magnetic resonance imaging"[tw] OR "functional mri"[tw] OR "functional mr"[tw] OR ("Magnetic Resonance Imaging"[mesh] AND "functional"[tw]) OR (("Magnetic Resonance Imaging"[mesh] OR MR imag*[tw] OR "MRI"[tw] OR "magnetic resonance"[tw]) AND ("Functional Neuroimaging"[Mesh:noexp] OR functional imag*[tw] OR functional neuroimag*[tw]))) AND ("Bipolar Disorder"[Mesh] OR "Bipolar and Related Disorders"[Mesh] OR "Bipolar Disorder"[tw] OR "Bipolar Disorders"[tw] OR "Manic-Depressive Psychosis"[tw] OR "Manic Depressive Psychosis"[tw] OR "Bipolar Affective Psychosis"[tw] OR "Manic-Depressive Psychoses"[tw] OR "Mania"[tw] OR "Manias"[tw] OR "Manic State"[tw] OR "Manic States"[tw] OR "Bipolar Depression"[tw] OR "Manic Disorder"[tw] OR "Manic Disorders"[tw] OR "manic depressive"[tw] OR "manic"[tw] OR Bipolar affectiv*[tw] OR Bipolar disease*[tw] OR Bipolar disorder*[tw] OR bipolar depress*[tw]) NOT ("Animals"[mesh] NOT "Humans"[mesh])

Figure 6.4: PRISMA Flow chart.
PRISMA flow chart of the literature search for included studies.



	BD patients	BD type	HC	BD patients	HC	Mood states	Medication	Task
	female n (%)	I/II (n)	female n (%)	mean age (SD)	mean age (SD)	(n)	Mood Stabilizers (n) Antipsychotics (n) Antidepressants (n)	
Emotion Tasks								
(Cerullo et al. 2014)[1]	25 (68%)	I (25)	25 (67%)	30.0 (8.0)	26.0 (7.0)	Depressed (25)	Unmedicated (25)	Modified continuous performance task emotional and neutral distracters (CPT-END)
(Mitchell et al. 2004)[2]	11 (0%)	NS (11)	13 (0%)	42.8 (1.8)	32,2 (3.6)	Not specified (11)	MS (9), AP (4), AD (5)	Emotional prosody task
(Wessa et al. 2007)[3]	17 (41%)	I (10), II (7)	17 (35%)	44.9 (12.7)	44.9 (13.4)	Euthymic (17)	MS (7), AP (8)	Affective go/no-go task
(Whalley et al. 2009)[4]	14 (29%)	I (14)	14 (26%)	35.4 (8.4)	38.4 (10.0)	Not specified (14)	MS (4), AP (8), AD (3)	Emotional memory task
(Young, Bodurka, and Drevets 2016)[5]	16 (88%)	I (16)	16 (88%)	37.6 (9.3)	37.8 (8.7)	Depressed (16)	Unmedicated (16)	Emotional autobiographical memory task
(Morris et al. 2012)[6]	13 (38%)	I (13)	15 (60%)	41.0 (3.0)	35.0 (2.0)	Euthymic (6); Hypomanic (5); Not specified (2)	AP (5), AD (6)	Emotion regulation task
(Zhang et al. 2020)[7]	15 (33%)	I (13), II (2)	15 (60%)	39.9 (12.5)	33.6 (11.1)	Depressed (2); Not specified (13)	AP (15), AD (9)	Emotion regulation task
(Han et al. 2018)[8]	10 (40%)	I (10)	10 (40%)	38.6 (9.4)	31.8 (8.0)	Euthymic (10)	MS (10), AD (8)	Emotional picture task
(Moser et al. 2018)[9]	37 (32%)	I (37)	48 (42%)	27.5 (8.1)	29.8 (8.5)	Not specified (27)	MS (15), AP (30), AD (7)	Emotion recognition task
(Kryza-Lacombe et al. 2019)[10]	33 (78%)	I (21), II (11)	22 (55%)	38.2 (11.1)	29.4 (7.2)	Depressed (8); Hypomanic (4); Mixed (1); Euthymic (44)	MS (29), AP (18), AD (15)	Face emotion labelling task
(Elliott et al. 2004)[11]	8 (50%)	I (7), II (1)	11 (73%)	35.0 (-)	37.6 (9.7)	Manic (8)	MS (7), AP (5)	Affective go/no-go task
(Foland et al. 2008)[12]	9 (66%)	I (9)	9 (66%)	34.6 (8.0)	30.4 (7.6)	Manic (9)	MS (8), AP (1)	Face emotion labelling task
(Lennox et al. 2004)[13]	10 (20%)	I (10)	12 (50%)	37.3 (12.8)	32.6 (10.7)	Manic (10)	MS (10), AP (8)	Face emotion labelling task
(Malhi et al. 2007)[14]	10 (100%)	I (10)	10 (100%)	33.5 (8.7)	33.6 (6.4)	Euthymic (10)	MS (7)	Explicit facial emotion recognition task
(Altshuler et al. 2008)[15]	11 (54%)	I (11)	17 (47%)	32.0 (7.3)	29.5 (6.6)	Depressed (11)	MS (8), AP (2), AD (3)	Face-matching task
(Chen et al. 2006)[16]	16 (19%)	I (16)	8 (75%)	Manic = 39 (13.4) Depressed = 41.9 (12.1)	38.75 (12.5)	Manic (8); Depressed (8)	MS (16), AP (6), AD (2)	Explicit and implicit face recognition task
(Jogia et al. 2008)[17]	12 (58%)	I (12)	12 (58%)	42.1 (11.8)	41.8 (10.9)	Not specified (12)	MS (12)	Sad affect face recognition task
(Hassel et al. 2008)[18]	19 (52%)	I (19)	24 (54%)	32.5 (8.8)	27.7 (8.7)	Euthymic (19)	MS (12), AP (14), AD (9)	Facial expression task
(Killgore, Gruber, and Yurgelun-Todd 2008)[19]	14 (21%)	NS (14)	13 (8%)	28.1 (11.2)	25.5 (4.7)	Not specified (14)	MS (5), AP (12), AD (1)	Fearful face perception task
(Lagopoulos and Malhi 2007)[20]	10 (100%)	I (10)	10 (100%)	33.6 (8.12)	33.6 (6.7)	Euthymic (10)	MS (7)	Emotional Stroop task

Continued on next page

Table 6.3 – continued from previous page

	BD patients	BD type	HC	BD patients	HC	Mood states	Medication	Task
	female n (%)	I/II (n)	female n (%)	mean age (SD)	mean age (SD)	(n)	Mood Stabilizers (n) Antipsychotics (n) Antidepressants (n)	
Reward Tasks								
(Abler et al. 2008)[21]	12 (42%)	I (12)	12 (42%)	33.9 (11.2)	36.2 (11.2)	Manic (8); Mixed (3); Hypomanic (1)	MS (12)	Monetary incentive task
Caseras et al. 2013)[22]	32 (59%)	I (17), II (15)	20 (65%)	42.3 (6.0)	41.6 (7.7)	Hypomanic (1); Euthymic (31)	MS (22), AP (12), AD (12)	Monetary reward processing task
(Chase et al. 2013)[23]	23 (82%)	I (23)	37 (67%)	33.9 (8.5)	33.1 (6.2)	Depressed (25)	MS (13), AP (11), AD (9)	Card number guessing task
(Frangou et al. 2008)[24]	7 (71%)	I (7)	7 (71%)	37.0 (5.9)	39.0 (5.9)	Euthymic (7)	MS (7)	Gambling task
(Jogia et al. 2012)[25]	36 (53%)	I (36)	37 (43%)	42.5 (10.6)	37.6 (11.3)	Euthymic (36)	Unmedicated (14), A (21), AP (6), AD (7)	Iowa gambling task
(Kirschner et al. 2019)[26]	25 (36%)	I (25)	25 (36%)	37.3 (9.1)	33.1 (9.7)	Euthymic (25)	MS (18), AP (18), AD (7)	Monetary incentive delayed task
(Manelis et al. 2019)[27]	34 (85%)	I (34)	17 (59%)	35.1 (1.3)	31.4 (1.5)	Depressed (16); Euthymic (18)	MS (10), AP (19), AD (15)	Card number guessing task
(Mason et al. 2014)[28]	20 (50%)	I (18), II (2)	20 (55%)	36.0 (4.3)	33.25 (9.3)	Euthymic (20)	MS (8)	Roulette task
(Sharma et al. 2016)[29]	24 (58%)		30 (55%)	38.0 (11.7)	39.4 (11.8)	Depressed (24)	MS (11), AP (11), AD (6)	Monetary reward procedure
Working Memory Tasks								
(Adler et al. 2004)[30]	15, unknown	I (15)	15, unknown	29.0 (9.0)	30.0 (9.0)	Euthymic (15)	Unmedicated (4) Unknown (11)	Letter n-back task
(Brooks et al. 2015)[31]	19 (42%)	II (19)	19 (52%)	36.7 (11.4)	42.6 (12.0)	Depressed (19)	Unmedicated (19)	Letter n-back task
(Deckersbach et al. 2008)[32]	9 (100%)	I (9)	17 (100%)	27.6 (2.8)	25.6 (5.9)	Depressed (9)	MS (9)	Letter n-back task (with mood induction)
(Drapier et al. 2008)[33]	20 (45%)	I (20)	20 (50%)	42.7 (10.4)	41.9 (11.6)	Euthymic (20)	MS (16), AP (4), AD (2)	Letter n-back tasks
(Fernández-Corcuera et al. 2013)[34]	41 (45%)	NS (41)	41 (41%)	40.4 (10.2)	40.3 (9.8)	Depressed (41)	Unmedicated (41)	Letter n-back task
(Frangou et al. 2008)[24]	7 (71%)	I (7)	7 (71%)	37.0 (5.9)	39.0 (5.9)	Euthymic (7)	MS (7)	Letter n-back task
(Gruber et al. 2010)[35]	18 (44%)	I (18)	18 (61%)	38.2 (9.9)	33.9 (11.5)	Euthymic (18)	Unmedicated (3) MS (12), AP (3), AD (6)	Verbal delayed-match-to-sample task
(Hamilton et al. 2009)[36]	21 (38%)	I (21)	38 (39%)	36.4 (10.7)	32.5 (11.7)	Euthymic (21)		Delayed match to sample task
(Jogia et al. 2012)[25]	36 (53%)	I (36)	37 (43%)	42.5 (10.6)	37.6 (11.3)	Euthymic (36)	Unmedicated (14) MS (21), AP (6), AD (7)	Letter n-back task
(Lagopoulos, Ivanovski, and Malhi 2007)[37]	10 (100%)	I (10)	10 (100%)	32.4 (10.8)	31.7 (11.9)	Euthymic (10)	MS (7)	Delay-response memory task
(McKenna et al. 2014)[38]	23 (65%)	I (23)	23 (65%)	45.3 (9.5)	44.8 (10.6)	Euthymic (23)	MS (17), AP (12), AD (11)	Pseudoword delayed match to sample task
(Monks et al. 2004)[39]	12 (100%)	I (12)	12 (100%)	45.8 (3.5)	45.6 (3.5)	Euthymic (12)	MS (12)	Letter n-back task Sternberg task

Continued on next page

Table 6.3 – continued from previous page

	BD patients	BD type	HC	BD patients	HC	Mood states	Medication	Task
	female n (%)	I/II (n)	female n (%)	mean age (SD)	mean age (SD)	(n)	Mood Stabilizers (n) Antipsychotics (n) Antidepressants (n)	
(Pomarol-Clotet et al. 2012)[40]	29 (37%)	I (29)	46 (41%)	49.8 (12.1)	36.3 (13.6)	Manic (n = 29)	MS (23), AP (24)	Letter n-back task
(Pomarol-Clotet et al. 2015)[41]	114 (54%)	I (108), II (6)	38 (52%)	39.9 (10.2)	39.7 (8.9)	Manic (38); Depressed (38); Euthymic (38)	MS (95), AP (69), AD (32)	Letter n-back task
(Robinson et al. 2009)[42]	15 (53%)	I (15)	15 (47%)	39.0 (12.6)	36.2 (10.6)	Euthymic (15)	MS (8), AP (7), AD (12)	Delayed-non-match-to-sample task
(Wu et al. 2014)[43]	20 (52%)	I (20)	29 (50%)	27.9 (6.4)	22.7 (5.1)	Not specified (n =20)	MS (18), AP (7), AD (12)	Letter n-back task
(Rodríguez-Cano et al. 2017)[44]	26 (61%)	I (26)	26 (61%)	45.6 (9.2)	46.8 (11.2)	Depressed (26)	MS (23), AP (14), AD (15)	Letter n-back task
(Moser et al. 2018)[9]	37 (32%)	I (37)	48 (42%)	27.5 (8.1)	29.8 (8.5)	Not specified (37)	MS (15), AP (30), AD (7)	Various stimuli n-back task
(Goikolea et al. 2019)[45]	31 (48%)	I (31)	31 (48%)	30.5 (9.1)	31.1 (8.8)	Manic (31)	MS (22), AP (31)	Letter n-back task
(Alonso-Lana et al. 2019)[46]	26 (42%)	I (26)	26 (42%)	39.2 (12.3)	40.2 (11.0)	Manic (baseline) (26); Euthymic (follow-up) (26)	MS (19), AP (22), AD (2)	Letter n-back task

Table 6.3: Descriptives of included fMRI studies of three domains of emotion processing, reward processing and working memory in the meta-analysis using a whole-brain approach. A total of 46 papers has been used including 49 fMRI studies.

NS = Not Specified, MS = Mood Stabilizers, AP = Antipsychotics, AD = Antidepressants.

CHAPTER 7

General Discussion

7.1 General Discussion

The main objective of the present thesis was to expand our knowledge of DB by investigating 1) endogenous and exogenous predictors of the development and course of the illness, 2) the complex interaction of mania and depressive symptoms, and 3) the long-term cognitive (dys)function and brain activity of patients with BD. First, in chapter 2 and 3 we examined predictors for the development and course of BD. Second, in chapter 4, we investigated the influence of external stressors, in particular the COVID-19 pandemic, on the stability of symptoms associated with the illness. Next, in chapter 5, we examined the complex interactions of symptoms of BD over time. Finally, in chapter 6, we reviewed neurocognitive functioning and brain functioning in BD.

This chapter provides a summary of the main findings, clinical implications, strengths and limitations, future research directions and a general conclusion. A common staging model will be used as an integrating principle to present the evidence.

7.1.1 Summary

In the chapters 2 and 3, we examined endogenous predictors of the onset and course of BD.

In **chapter 2**, we investigated whether personality traits independently predicted the occurrence of (hypo)mania in a group of patients with depressive or anxiety disorder. We used survival analysis to investigate the influence of personality traits on the incidence of (hypo)manic symptoms and episodes during the 9-year follow-up. Our results indicated that low agreeableness was a personality-related risk factor that could anticipate the development of a (hypo)manic episode or associated symptoms.

Another (somewhat related) prodromal feature for conversion to BD is feelings of anger. Feelings of anger and irritability are prominent symptoms of BD that may occur during hypomanic, depressive, and, especially, during mixed mood states. In addition, some symptoms of BD, including irritability, anger, and emotional instability, overlap with personality disorders, such as borderline personality disorder and antisocial personality disorder. In **chapter 3**, we cross-sectionally examined different constructs of anger and cluster B personality traits. Prospectively, we investigated the predictive value of aggression reactivity in the conversion from depression to BD during the 9-year follow-up. Our study demonstrated a strong and consistent relationship both in the cross-sectional and in the prospective analysis. Higher levels of anger in all its variants were consistently associated with bipolarity. In our prospective findings, aggression reactivity was a risk factor for the conversion to BD in persons with a history of unipolar depression. Patients with unipolar depression who show higher levels of anger and aggression might be particularly at risk for the development of BD.

In the **4th Chapter**, we conducted a longitudinal investigation of the impact of COVID-19 measures on young adults recently diagnosed with BD, using an existing cohort from the BINCO study. This study aimed to compare the levels of symptoms related to mania, depression, anxiety, and stress before and during the pandemic, using up to six follow-up measurements in relatively young patients with BD. The results of our study revealed a significant increase in observer-rated (hypo)mania symptoms during the first two months of the pandemic when compared to the (hypo)mania levels observed before the pandemic.

Manic and depressive mood states in BD may emerge from the non-linear relations between constantly changing mood symptoms exhibited as a complex dynamic system. The interactions between these symptoms can be captured using the Dynamic Time Warp (DTW) algorithm, which is capable of analyzing panel data with sparse observations over time. In **Chapter 5**, we used DTW to analyze the dynamics of symptoms over time and utilized symptoms of BD that were collected repeatedly (every 3 to 6 months) to assess depression and manic symptoms in 141 patients with BD. Idiographic symptom networks were highly variable between patients. Despite this individual variability, our group-level analyses revealed five symptom dimensions based on prospective data in which individuals were analyzed first, before the data were aggregated (core [hypo]mania, dysphoric mania, lethargy, somatic/suicidality, and sleep). The identification of these five symptom dimensions acknowledges the variability of clinical states that fall within the bipolar syndrome, which is much more complex than simply being either in a manic or depressed state. Moreover, we analyzed the temporal dynamics between the five symptom dimensions. Symptoms of the 'Lethargy' dimension showed the highest out-strength, and its changes preceded those of 'somatic/suicidality', while changes in 'core (hypo)mania' preceded those of 'dysphoric mania'. Thus, a state of 'lethargy' seems to temporally follow a state 'somatic/suicidality' or vice versa, that improvements in 'lethargy' were followed by improvements in the 'somatic/suicidality' domain. Similarly, decreases and increases in the 'dysphoric mania' domain tended to be followed by similar changes in the 'dysphoric mania' domain.

In addition to affective symptoms, patients with BD may show cognitive impairments and emotion regulation deficits during episodes and also during euthymia. In **chapter 6**, we conducted a meta-analysis of fMRI studies in patients with BD, investigating emotion processing, reward processing and working memory, domains which all rely on proper fronto-limbic network activity. Our findings revealed significant differences in brain activity in BD patients, as compared to healthy controls, mostly within the fronto-limbic network. BD patients showed hyperactivation in the amygdala and hippocampus and hypoactivation in the inferior frontal gyrus during emotion processing, hyperactivation in the orbitofrontal cortex during reward processing, and hyperactivation in the prefrontal cortex and anterior cingulate cortex during working memory activity. Interestingly, limbic activation alterations were only manifested in euthymic BD patients, whereas more widespread frontal dysfunctions were also found during depression and mania. This suggests that aberrant limbic activity during cognitive and emotion processing may be a trait-related BD characteristic; on the other hand, disruptions in frontal cortex activity may be associated with state-related factors.

7.1.2 Integrating the evidence: the staging models

In this dissertation, we have studied different aspects of bipolar disorder from different perspectives. As an organizing principle, it can be helpful to describe the chapters in the context of a common staging model of BD. The model is based on evidence that considers BD as a neuroprogressive disorder. The general idea is that as the illness progresses over time, it will manifest more prominent changes at the clinical and neuropathological level, ultimately leading to treatment resistance and cognitive deficits[1]. The staging model of BD assumes that the disease progresses through a more or less predictable path, starting at an at-risk or latency stage 0, then a prodromal stage 1 that may progress to a first clinical threshold episode in stage 2, one or more recurrences in stage 3 with the potential to revert or progress to late or end-stage manifestations in stage 4[2]. Staging models aim to be a tool for clinicians to describe the course of BD and provide a potential framework for interventions for individual patients. Although several staging models[3, 4, 5, 6, 7, 8] have been proposed for BD, we will focus here on the classic models of Berk et. al (2007)[7] and Kapczinski et al. 2009[8](see Table 1). The model introduced by Berk et. al (2007) (further called “model A") is based on the occurrence and recurrence of mood episodes, whereas the model of Kapczinski et al. 2009 (further called “model B") is defined by intra-episodic functional impairment. As the work progresses over the chapters, we started our journey with investigations of patients with BD in a relatively early phase of staging where the disease has not yet manifested itself, subsequently examining symptomology and the course of BD, and we ended in the final stage with the investigation of brain dysfunction of BD patients with noticeable long-term emotional and cognitive impairments.

In chapters 2 and 3, we investigated prodromal features (risk factors), personality traits, and anger in the development of BD. These two chapters fit best with the staging phase 1b of model A, the prodrome stage (Table 1). In chapter 4, we examined the effects of COVID-19 on patients with recently diagnosed bipolar disorder, which best corresponds with stage 2; ’First-episode mood disorder’ of model A. In chapter 5 we investigate the dynamic interactions of depressive and manic symptoms over time. In this study, we examined patients with BD who had the disease for some time and often had multiple episodes. Therefore, chapter 5 fits best in phase 3C of multiple relapses of model A. Finally, in our fMRI meta-analysis, we investigated the dysfunction of brain activity in patients with BD. This chapter fits best in stages 3 and 4 of models A and B, in particular model B, because this model includes impairment in cognition or functioning.

Stage	Model A Berk et al. (2007)[7]	Model B Kapczinski et al. (2009)[8]	Thesis Chapters
0	Increased risk of severe mood disorder (e.g., family history, abuse, substance use). No specific symptoms currently.	At risk for developing BD, positive family history, mood or anxiety symptoms without criteria for threshold BD.	
1a	Mild or non-specific symptoms of mood disorder.	Well-defined periods of euthymia without overt psychiatric symptoms.	
1b	Prodromal features: ultra high risk.		2 & 3
2	First-episode threshold mood disorder.	Symptoms in interepisodic periods related to comorbidities.	4
3a	Recurrence of sub-threshold mood symptoms.	Marked impairment in cognition or functioning.	
3b	First threshold relapse.		
3c	Multiple relapses.		5 & 6
4	Persistent unremitting illness.	Unable to live autonomously owing to cognitive and functional impairment.	6

Table 7.1: Models for staging in BD.

7.1.3 Prodromal features: Stage 1

In chapters 2 and 3, we examined endogenous predictors of the onset and course of BD that can be considered as prodromal features, or ultra-high risk corresponding with stage 1b of Berk et al. (2007). This stage includes patterns of onset of sub-threshold symptoms or mood fluctuations with comorbid symptoms of anxiety or major depressive episode with predictors of polarity. One of the difficulties faced by the field involves discovering a prodromal signature that might have predictive diagnostic value and support a distinct therapeutic strategy. There are claims that specific indicators and symptoms are common during the prodromal phase. These include a family history of bipolarity, suicide attempts, early age of onset, atypical characteristics such as hypersomnia, postpartum episodes, severe premenstrual syndrome, melancholic psychotic features, a seasonal pattern, a flattened or lacking energy demeanor, and noticeable irritability[9, 10].

We investigated the predictive value of personality traits and anger since earlier cross-sectional studies indicated a strong association between these predictors and BD. In addition, these factors had not previously been investigated as potential risk factors or prodromal features for conversion to BD. We examined these prodromal features of BD in a longitudinal study focusing on depression, in which a subset of patients eventually progressed to BD.

BD is often missed or misdiagnosed by clinicians; this is illustrated by an average treatment delayof up to 10 years after the first major mood episode[11]. Although the criteria for classifying (hypo)mania in patients with BD and unipolar depressive disorder are very clear, it is often not obvious in clinical practice. BD patients start often with predominantly depressive episodes, which are usually later followed by (hypo)manic episodes[12]. Earlier studies showed the 5-year rate for conversion to BD is about 20%[13]. An unjustified diagnosis of unipolar disorder can have major disadvantages such as inadequate pharmacological treatment. Inadequate pharmacological treatments are associated with an increased risk of recurrence, non-response, longer illness duration, and possible induction of (hypo)mania[14]. The delay in initiating effective treatment may also result in hospital admissions, longer admission durations, and an elevated risk of suicide[15]. Hence, it is crucial to differentiate between BD and unipolar disorder and accurately identify BD.

Our findings relating to certain personality traits (low agreeableness) and anger could indicate potential indications of BD, along with clinical features multiple brief depressive episodes and a family history of BD.

Based on current and previous findings, it can be cautiously concluded that that especially anger and aggression dysregulation are the most distinct affective characteristics for BD when compared to unipolar depression. One possible explanation for this is the presence of mixed mood states. Although further research is needed, the occurrence of agitated or mixed depression in unipolar depression may indicate an early sign of BD conversion, as mixed episodes are more common in BD patients.

First episode: Stage 2

In stage 2, the first episode could present a critical window for timely and suitable intervention. Both misdiagnosis and initiation of inappropriate therapy can worsen the course of BD[7]. Having an understanding of the circumstances that may influence the course of a disease is crucial. Chapter 4 examined the impact of COVID-19 on individuals who have been recently diagnosed with BD. This group corresponds with stage 2 of model A, which is characterized as "first-episode mood disorder." The COVID-19 pandemic has had a significant impact on individuals with BD, as well as the general population. The observed increase in manic symptoms among the younger-aged cohort in our study, in contrast to the findings of a previous study[16] that reported a decrease in manic symptoms among older patients with BD, may be attributed to the vulnerability of younger individuals with BD to life stressors in comparison to older adults. This phenomenon can be explained by the inoculation hypothesis, which posits that older adults are better equipped to cope with life stressors due to their greater life experience[17]. Given that the observed increase in (hypo)manic symptomatology in the current sample was relatively mild and did not result in any severe manic (psychotic) decompensations, it can be interpreted as a potential indicator of resilience and adaptability among this population, as previously proposed[18]. However, it is crucial to note that the increase in symptoms highlights the need for close monitoring of individuals with BD, even during lockdown measures and future national or international crises.

Recurrence: Stage 3

BD advances from prodrome to onset and later to chronicity in stage 2 to 3. In this stage the interrelationship between symptoms or episodes can be studied, in particular from the idea that some symptoms can be more central to an episode and potentially predict other symptoms. Insight into the temporal directional relationships between mood symptoms (either depression or mania), both in individuals and groups of patients with BD, may enable more personalized approaches to treatment. In **chapter 5**, we used DTW, which is a novel data-analytical approach for psychiatry, to investigate interactions and relative changes in symptom severity within and between patients with BD over time. DTW is a computational algorithm that can be used to process individual symptom data and takes potential non-linear dynamics among symptoms into account[19, 20]. It focuses on profiles of change in time series data rather than absolute levels of symptom scores. This method helped us to investigate the symptom interconnection within longitudinal data, even when there are only sparse numbers of time points. We provided individual-level (i.e., idiographic) and group-level (i.e., nomothetic) analyses.

The individual patient analysis revealed significant diversity across patients in symptom presentation over time. The group-level analyses identified five symptom dimensions, namely core (hypo)mania, dysphoric mania, lethargy, somatic/suicidality, and sleep. The identification of these 5 symptom dimensions acknowledges the variability of clinical states that fall within bipolar syndrome, which appeared to be much more complex than simply being either manic or depressive. The symptom dimension referred to as 'core (hypo)mania' appears to correspond to the traditional manic state characterized by heightened energy, excessive activity, and a euphoric mood. The dimension labeled as 'dysphoric mania' is typically indicative of a mixed mood state, as previously described in literature[21, 22], wherein energy levels are heightened while the mood is marked by irritability and agitation. Prior studies have suggested that this psychiatric state constitutes a critical juncture in which patients undergo a transitional phase from depression to mania, or vice versa, yet become ensnared in a persistent "switch" state[23]. Based on current data, it appears that 'dysphoric mania' typically follows 'core (hypo)mania' in a temporal sequence, indicating that a manic state often progresses into a mixed state over time. Conversely, a reverse pattern may also occur, whereby as pure manic symptoms subside, dysphoric symptoms subsequently decrease as well. The two symptom dimensions, 'lethargy' and 'somatic/suicidality' are positioned in the depressive pole. The dimension 'lethargy' consists of typical depressive symptoms, and it precedes increases in symptom severity in the 'somatic/suicidality' dimension. This implies that treatment could perhaps primarily focus on the 'lethargy' symptoms to reduce 'somatic/suicidality' symptoms.

Impairment in cognition or functioning: Stages 3 & 4

The adverse effects of recurrent mood episodes in bipolar disorder, compounded by life stressors and insufficient coping mechanisms, can lead to cumulative neural dysfunction in patients with BD. Neurocognitive impairments appear to be present to some degree in the majority of patients with BD in the early course. However, cognitive function tends to increase with the duration of the illness, the number of mood episodes, and hospital admission. These cognitive deficits tend to be preserved in a euthymic state and may be considered a trait-related characteristic of BD. Our fMRI meta-analysis (chapter 6) aimed to investigate the patterns of brain activity dysfunction in individuals with BD in three different domains of emotion processing, reward processing, and working memory. This chapter aligns most closely with stages 3 and 4 of models A and B, specifically model B, as it encompasses the impairment in cognitive functioning. During emotion processing tasks, individuals with BD displayed hyperactivity in limbic regions (the amygdala and hippocampus), as well as hypoactivity in the frontal region (inferior frontal gyrus), when compared to healthy subjects. Our results suggest that limbic hyperreactivity and reduced enrolment of prefrontal brain regions might explain the deficiencies in emotional processing in BD. We found increased activity in the left orbitofrontal cortex during reward processing. This region is crucial for coding pleasure and processing reward outcomes. Our study found increased activity in the subgenual ACC and ventromedial PFC during working memory tasks compared to healthy controls. These regions are connected to limbic structures and involved in reward valuation, emotion regulation, and cognitive integration. The ventromedial PFC connects the amygdala with the dorsolateral PFC, regulating the effects of working memory load and emotional interference. Similarly, the subgenual ACC acts as a bridge between the dorsolateral PFC and amygdala, contributing to emotional processing and attention. Limbic hyperactivation was only found during euthymia in emotion and reward processing domains; abnormalities in frontal cortex activity were also found in BD patients with mania and depression. This might suggest that poor frontal inhibitory control may be more evident during depressive or manic episodes, while increased limbic sensitivity may only occur during euthymia and could be a risk factor for provoking mood episodes.

To the best of our knowledge, this is the first meta-analysis showing robust fronto-limbic network abnormalities in emotion and cognitive processing during both in euthymic as well as symptomatic patients. The differentiation of three cognitive domains in relation to fronto-limbic network functioning in BD allowed a better perspective on how neurocognitive abnormalities can co-exist in parallel.

7.1.4 Clinical implications

The use of a staging model for BD can help to define clinical needs and guide treatments and prognosis. From this staging perspective, we can classify the clinical implication of this thesis. In the first part, we mainly studied prodromal stage 1 features. Identifying the potential risk factors or prodromal features for the development of BD might have clinical value in earlier recognition, prevention of conversion into mania, and better-targeted interventions. Our findings showed that low agreeableness and anger are risk factors for conversion to BD. In the clinical setting, a patient's assessment that reveals high emotional instability, with more feelings of anger and a tendency to disagree, compete, and be suspicious, could indicate a heightened risk[24]. Our findings are consistent with the idea that in clinical practice, BD patients tend to be less agreeable, which might be associated with less willingness to follow advice. Also, BD patients experience extensive emotional instability even during euthymic states[25] and seem to use maladaptive strategies such as rumination[26]. It is important that patients learn to regulate such feelings in an appropriate way. Psychotherapy, social therapy, and group-oriented approaches can help BD patients to prevent decompensation and to develop healthier social relationships. Other treatment strategies that may especially be apt to improve emotion regulation are dialectical behavior therapy and systems training for emotional predictability and problem-solving program, which is based on cognitive behavioral therapy combined with emotional management skill training[27].

Understanding the impact of environmental stressors, such as life stress, on the progression of BD is crucial during the early clinical stage 2 of the illness. Our conclusion based on the results of COVID-19 showed an increase in (hypo)manic symptomatology in recently diagnosed BD patients during the initial phases of the COVID-19 pandemic compared to pre-pandemic symptomatology. Closely monitoring the symptoms during stressful life events can help timely interventions to prevent aggravation of symptoms or full decompensation.

BD progresses from prodrome to onset and ultimately to chronicity in stages 2 to 3. Despite the heterogeneity of symptomatology, cycling patterns, and severity of episodes, the patterns of recurrence within a patient tends to follow the same pattern. The most important clinical value of our DTW network approach is the unique individual profiles that DTW can provide. Patient-level analyses can, in principle, be used to construct a personalized profile of the dynamic relationship between the individual symptoms. Such personal symptom profiles could enable patients and their caregivers to gain more insight into their symptom dynamics, depicting which change in one dimension precedes that of other dimensions. It may also help clinicians in decision-making and personalized treatment when a network is constructed based on Ecological momentary assessment (EMA) data gathered in a single patient. However, for this promising application, more research on individual-level analyses is needed. In the future, we hope that with sufficient assessments the individual-level analysis might help to identify early warning symptoms of a new episode in the treatment. The symptoms with the highest out-strength score could be promising targets in personalized treatment to prevent a more severe mood state. For instance, if a patient has central symptoms with the highest scores on 'early morning insomnia' and 'sad mood', these two symptoms could be primarily targeted in the intervention as these symptoms potentially could develop into other symptoms, resulting in a more severe episode. The large variation between individuals in our patient group underline that the clinical states of bipolar syndrome is much more complex than just the two poles of either mania or depression.

Evidence has shown cognitive and functional decline along with the progression of BD. In particular, patients in stages 3 (recurrence) and 4 (cognitive and functional impairments) performed worse than healthy controls in several neurocognitive domains[28]. By detecting altered brain activation in BD, we might get more understanding of the underlying mechanisms of symptoms and characteristics of BD. Such differences in brain activity might explain certain complaints and symptoms of BD that we can observe at the behavioral level and eventually help us to target therapeutic interventions. For instance, reward processing dysfunction is relatively new as an underlying mechanism in BD. It is known that patients with BD show motivational and behavioral (impulsive and risk-taking) problems which are associated with reward processing in the brain. Results from our metanalysis confirm that motivational and impulsive/risk taking behavior are also apparent on a neurological level. This underlines the importance in the clinical setting to pay attention to these problems, for example in psycho-education on how to signal these symptoms and how to deal with them.

7.1.5 Strengths and limitations

One of the strengths of the present thesis is that we attempted to investigate the development and the course of BD from different angles to study the onset and the course of BD, integrating insight and different methods.

Regarding the NESDA studies (chapter 2 and 3), the most important strengths are the large sample size and the long follow-up period (9 years). Another strength of NESDA studies is its longitudinal design and the inclusion of a large group of participants that oversampled patients with (preceding) depression, which made it possible for us to study the predictors for conversion to BD. A strength of the COVID study (chapter 4) is the preexisting data that made it possible to examine and compare symptoms in the same BD patients both before and during the COVID-19 pandemic. A strength of our network approach with DTW is that for the first time it allowed an intricate analysis of the complex temporality of symptoms in various mood states. Finally, our meta-analysis was the first to show robust fronto-limbic network abnormalities during emotion, reward, and cognitive functioning. We were able to demonstrate that the fronto-limibic network is thoroughly affected in BD, both in euthymic as well as symptomatic patients, which suggests both trait and state differences in BP brain functioning.

A main limitation of this thesis concerns the long-time intervals between measurements in the longitudinal studies (NESDA and the Bipolar stress Study). This means that possible relapse or remission in between intervals is unknown. Also, individuals with more severe depressive and manic symptoms were underrepresented in our studies. Further studies with shorter time intervals, with individuals with more severe depressive and manic symptoms are needed. EMA with BD patients is needed to allow studies with much shorter time intervals between measurements. EMA uses mobile devices such as smartphones to assess a range of physical and mental experiences at different moments throughout the day[29] and such data is increasingly used to characterize patients' daily lives, monitor mood, and test the efficacy of treatment interventions. Yet, many BD patients in a current episode may be incapable of completing daily or even weekly assessments.

A limitation of our fMRI analysis is that the number of BD subjects for the different states was limited. This may have resulted in the negative finding of limbic activity during affective states. Future studies specifically focusing on state-related emotional and cognitive functioning are required to increase the power of meta-analyses.

7.1.6 Research implications and future directions

In the current dissertation, most of the studies (except for the fMRI meta-analysis) were based on longitudinal data analyses. The longitudinal studies have proven their great value for in BD. One of the benefits of a longitudinal study is the ability to identify developments or particular changes in the characteristics of BD (at both individual and group levels). In other words, it extends beyond a single moment in time by establishing sequences of events. The studies in the current thesis contribute to expanding our knowledge by using different approaches, such as DTW to investigate and interpret the complex longitudinal symptom associations in BD. Next, we performed an fMRI meta-analysis because the heterogeneity of imaging findings limits their importance for the understanding of the pathophysiology of BD. By performing an fMRI meta-analysis, we aimed to aggregate the evidence to draw more rigorous conclusions regarding the potential abnormalities in the fronto-limbic network in BD.

Conducting research across all phases of BD is essential from a staging perspective. This allows for a better understanding of the disorder's progression and facilitates the development of targeted interventions. To start, longitudinal studies following at-risk patients as well as first-onset BD patients are needed because they offer the ability to prospectively detail the emerging psychopathologic condition and provide for comparison between at-risk offspring who become affected and those who do not become affected. In line with this, longitudinal neuroimaging studies following at-risk patients as well as first-onset BD patients are needed to examine the development of cognitive impairments and their association with fronto-limbic findings over the course of BD. In order to investigate prodromal features that affect the development and course of BD, larger and more longitudinal studies are needed. In addition, we need more nationwide large cohorts, like NESDA, to study BD from different angles over time to study the course of the disease.

The ongoing BINCO research with recently diagnosed will expand our knowledge of BD by investigating the biological, neurological, psychological, and environmental factors from the start of treatments. In this study, lifestyle and psychological factors in combination fMRI and omics data such as metabolomics and microbiome are collected, which can help us to understand the link between these biological and environmental factors. In parallel, we need research examining treatment effects (psychotherapy and pharmacotherapy) on the course, mood fluctuations, cognitions, and, importantly, the quality of life of patients with BD. The models on BD are mainly based on biological theories; however, recent studies have shown that psychotherapeutic interventions are beneficial in terms of symptom reduction, episode prophylaxis, and improvement of adherence and psychosocial functioning[30]. This field of psychology in BD is still relatively unexplored and needs more future research.

Moreover, future network analyses based on new technics such as DTW are needed, which view these disorders as complex dynamic systems rather than as a disorder with an underlying common cause. They hopefully can form a bridge between science and clinical setting in the sense that they can be applied to better map individual symptoms strategies over time to target appropriate treatment. Preferably, in the future DTW and EMA can be combined to examine the link between physiological and psychological factors, such as emotion and stress or sleep, with short time-interval (daily or weekly). Finally, longitudinal neuroimaging studies in patients who suffer from cognitive impairments are needed to examine the long-term alternations in brain activity patterns to understand the progression of the illness and, to provide more targeted treatments in this late or end stage of BD.

7.2 General conclusion

In sum, in this dissertation we investigated BD from different angles. By studying predictors and interconnection of symptoms over time in BD we expanded our knowledge about the recognition of risk factors, prevention of conversion into mania, early alarm symptoms of decompensation, and potentially better-targeted interventions. By investigating brain characteristics of BD, we got more insight into state and trait alternations in brain activity patterns which can help to better understand underlying mechanism of mood dysregulations and cognitive deficiencies in BD. To return to our research questions:

What are endogenous and exogenous predictors for the development and course of BD?

In this dissertation, we demonstrated that personality traits low agreeableness and anger are endogenous predictors for conversion in BD, and COVID-19 as an exogenous predictor, was a trigger for (hypo)manic symptoms in BD.

How are symptoms of BD interconnected, and how do they interact over time?

We investigated interactions and relative changes in symptom severity in patients with BD and showed that symptoms affect and interact with each other. On an individual level, we showed how heterogeneous these symptom profiles are, and on group levels, we demonstrated how five dimensions interacted over time.

Do BD patients show aberrant brain activity function compared to healthy controls?

We demonstrated that BD patients showed dysfunction of the fronto-limbic network, present in both euthymic and symptomatic patients.

With this dissertation, we add to the small research steps that are needed better understand the etiology, symptomatology, and neurobiology of BD, with the ultimate aim to aid in the diagnosis and personalized treatment of patients with.

Bibliography

1. Salagre E et al. “Toward Precision Psychiatry in Bipolar Disorder: Staging 2.0”. In: *Front. Psychiatry* 9 (2018), p. 641.
2. Martino DJ, Samamé C, Marengo E, Igoa A, and Strejilevich SA. “A critical overview of the clinical evidence supporting the concept of neuroprogression in bipolar disorder”. In: *Psychiatry Res.* 235 (2016), pp. 1–6.
3. Fava GA and Kellner R. “Staging: a neglected dimension in psychiatric classification”. In: *Acta Psychiatr. Scand.* 87.4 (1993), pp. 225–230.
4. Duffy A, Alda M, Hajek T, Sherry SB, and Grof P. “Early stages in the development of bipolar disorder”. In: *J. Affect. Disord.* 121.1-2 (2010), pp. 127–135.
5. Post RM. “Mechanisms of illness progression in the recurrent affective disorders”. In: *Neurotox. Res.* 18.3-4 (2010), pp. 256–271.
6. Reinares M et al. “Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome”. In: *J. Affect. Disord.* 144.1-2 (2013), pp. 65–71.
7. Berk M et al. “Setting the stage: from prodrome to treatment resistance in bipolar disorder”. In: *Bipolar Disord.* 9.7 (2007), pp. 671–678.
8. Kapczinski F et al. “Clinical implications of a staging model for bipolar disorders”. In: *Expert Rev. Neurother.* 9.7 (2009), pp. 957–966.
9. Faedda GL, Baldessarini RJ, Glovinsky IP, and Austin NB. “Pediatric bipolar disorder: phenomenology and course of illness”. In: *Bipolar Disord.* 6.4 (2004), pp. 305–313.
10. Álvarez-Cadenas L et al. “Detection of bipolar disorder in the prodromal phase: A systematic review of assessment instruments”. In: *J. Affect. Disord.* 325 (2023), pp. 399–412.
11. Drancourt N et al. “Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment”. In: *Acta Psychiatr. Scand.* 127.2 (2013), pp. 136–144.

12. Faedda GL et al. “An International Society of Bipolar Disorders task force report: Precursors and prodromes of bipolar disorder”. In: *Bipolar Disord.* 21.8 (2019), pp. 720–740.

13. Goldberg JF, Harrow M, and Whiteside JE. “Risk for bipolar illness in patients initially hospitalized for unipolar depression”. In: *Am. J. Psychiatry* 158.8 (2001), pp. 1265–1270.

14. Ghaemi SN, Boiman EE, and Goodwin FK. “Diagnosing Bipolar Disorder and the Effect of Antidepressants. A Naturalistic Study”. In: 61 (2000), pp. 804–808. ISSN: 0160-6689.

15. Baldessarini RJ, Pompili M, and Tondo L. “Suicide in bipolar disorder: Risks and management”. In: *CNS Spectr.* 11.6 (2006), pp. 465–471.

16. Orhan M et al. “Psychiatric symptoms during the COVID-19 outbreak in older adults with bipolar disorder”. In: *Int. J. Geriatr. Psychiatry* 36.6 (2021), pp. 892–900.

17. Knight BG, Gatz M, Heller K, and Bengtson VL. “Age and emotional response to the Northridge earthquake: a longitudinal analysis”. In: *Psychol. Aging* 15.4 (2000), pp. 627–634.

18. Stefana A et al. “The COVID-19 pandemic is a crisis and opportunity for bipolar disorder”. In: *Bipolar Disord.* 22.6 (2020), pp. 641–643.

19. Hebbrecht K et al. “Understanding personalized dynamics to inform precision medicine: a dynamic time warp analysis of 255 depressed inpatients”. In: *BMC Med.* 18.1 (2020), p. 400.

20. Booij MM et al. “Dynamic time warp analysis of individual symptom trajectories in depressed patients treated with electroconvulsive therapy”. In: *J. Affect. Disord.* 293 (2021), pp. 435–443.

21. Akiskal HS and Benazzi F. *Toward a clinical delineation of dysphoric hypomania - operational and conceptual dilemmas.* 2005.

22. Dilsaver SC, Chen YR, Shoaib AM, and Swann AC. “Phenomenology of mania: evidence for distinct depressed, dysphoric, and euphoric presentations”. In: *Am. J. Psychiatry* 156.3 (1999), pp. 426–430.

23. Malhi GS, Fritz K, Elangovan P, and Irwin L. “Mixed States: Modelling and Management”. In: *CNS Drugs* 33.4 (2019), pp. 301–313.

24. Chapman BP. “Bandwidth and Fidelity on the NEO-Five Factor Inventory: Replicability and Reliability of Item Cluster Subcomponents”. In: *Journal of Personality Assessment* 88.2 (2007), pp. 220–234.

25. Henry C et al. “Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period”. In: *Psychiatry Res.* 159.1-2 (2008), pp. 1–6.

26. Dodd A, Lockwood E, Mansell W, and Palmier-Claus J. “Emotion regulation strategies in bipolar disorder: A systematic and critical review”. In: *J. Affect. Disord.* 246 (2019), pp. 262–284.

27. Eisner L et al. “Dialectical Behavior Therapy Group Skills Training for Bipolar Disorder”. In: *Behav. Ther.* 48.4 (2017), pp. 557–566.

28. Rosa AR et al. “Clinical staging in bipolar disorder: focus on cognition and functioning”. In: *J. Clin. Psychiatry* 75.5 (2014), e450–6.

29. Shui X et al. “A dataset of daily ambulatory psychological and physiological recording for emotion research”. In: *Sci Data* 8.1 (2021), p. 161.

30. Miklowitz DJ. “Adjunctive psychotherapy for bipolar disorder: state of the evidence”. In: *Am. J. Psychiatry* 165.11 (2008), pp. 1408–1419.

CHAPTER 8

Appendix

8.1 Nederlandse Samenvatting

Het belangrijkste doel van dit proefschrift was om onze kennis van bipolaire stoornis (BS) uit te breiden door het onderzoeken van 1) endogene en exogene voorspellers van de ontwikkeling en het beloop van de ziekte, 2) de complexe interactie van manie en depressieve symptomen en 3) de lange-termijn cognitieve (dis)functie en hersenactiviteit van patiënten met BS. Ten eerste hebben we in hoofdstuk 2 en 3 voorspellers voor de ontwikkeling en het beloop van BS onderzocht. Ten tweede hebben we in hoofdstuk 4 de invloed van externe stressoren onderzocht, met name de COVID-19 pandemie, op de stabiliteit van symptomen die verband houden met de ziekte. Vervolgens hebben we in hoofdstuk 5 de complexe interacties van symptomen van BS in de loop van de tijd geanalyseerd. Tot slot hebben we in hoofdstuk 6 neurocognitief functioneren en hersenfunctie in BS onderzocht.

In **hoofdstuk 2** hebben we bestudeerd of persoonlijkheidstrekken onafhankelijk voorspellend waren voor het optreden van (hypo)manie bij een groep patiënten met een depressieve of angststoornis. We hebben "Survival analyse" gebruikt om de invloed van persoonlijkheidstrekken op het voorkomen van (hypo)manische symptomen en episoden gedurende de 9-jarige follow-up te onderzoeken. Onze resultaten wezen erop dat lage meegaandheid (agreeableness) een persoonlijkheidsgerelateerde risicofactor was die de ontwikkeling van een (hypo)manische episode of bijbehorende symptomen kon voorspellen.

Een andere (enigszins gerelateerde) prodromale eigenschap voor de conversie naar BS zijn gevoelens van boosheid. Gevoelens van boosheid en prikkelbaarheid zijn prominente symptomen van BS die kunnen optreden tijdens (hypo)mane, depressieve en vooral gemengde stemmingstoestanden. Bovendien overlappen sommige symptomen van BS, waaronder prikkelbaarheid, boosheid en emotionele instabiliteit, met persoonlijkheidsstoornissen zoals borderline- en antisociale persoonlijkheidsstoornis. In **hoofdstuk 3** hebben we in een cross-sectioneel onderzoek naar relatie tussen BS en verschillende constructen van boosheid en cluster B-persoonlijkheidstrekken. Prospectief hebben we de voorspellende waarde van boosheid onderzocht bij de conversie van depressie naar BS gedurende de 9-jarige follow-up. Onze studie toonde een sterke en consistente relatie aan, zowel in de cross-sectioneel-analyse als in de prospectieve analyse. Hogere niveaus van boosheid in al zijn varianten werden consequent geassocieerd met bipolairiteit. In onze prospectieve bevindingen was boosheid een risicofactor voor de conversie naar BS bij personen met een voorgeschiedenis van unipolaire depressie. Patiënten met unipolaire depressie die hogere niveaus van boosheid en agressie vertonen, lopen mogelijk risico op de ontwikkeling van BS.

In **hoofdstuk 4** hebben we een longitudinaal onderzoek uitgevoerd naar de impact van COVID-19-maatregelen op jongvolwassenen die recentelijk de diagnose BS hebben gekregen, met behulp van een bestaand cohort uit de BINCO-studie. Deze studie had tot doel de niveaus van symptomen gerelateerd aan manie, depressie, angst en stress te vergelijken vóór en tijdens de pandemie, met behulp van maximaal zes follow-upmetingen bij relatief jonge patiënten met BS. De resultaten van onze studie toonden een significante toename van scores van (hypo)manische symptomen gedurende de eerste twee maanden van de pandemie in vergelijking met de (hypo)manie-scores die vóór de pandemie werden waargenomen.

Manische en depressieve stemmingstoestanden bij BS kunnen voortkomen uit de niet-lineaire relaties tussen voortdurend veranderende stemmingsymptomen die zich manifesteren als een complex dynamisch systeem. De interacties tussen deze symptomen kunnen worden vastgelegd met behulp van het Dynamic Time Warp (DTW) algoritme, dat in staat is om paneelgegevens met spaarzame observaties in de tijd te analyseren. In **hoofdstuk 5** hebben we DTW gebruikt om de dynamiek van symptomen in de tijd te analyseren en symptomen van BS die herhaaldelijk werden verzameld (elke 3 tot 6 maanden) te meten bij 141 patiënten met BS. Idiografische symptoomnetwerken (onderlinge) verschilden sterk tussen patiënten. Ondanks deze individuele variabiliteit onthulden onze groepsanalyses vijf symptoomdimensies (kern [hypo]manie, dysfore manie, lusteloosheid, somatisch/suïcidaliteit en slaap) op basis van prospectieve gegevens waarbij individuen eerst werden geanalyseerd voordat de gegevens werden geaggregeerd. De identificatie van deze vijf symptoomdimensies erkent de variabiliteit van klinische toestanden die binnen het bipolaire syndroom vallen, wat veel complexer blijkt te zijn, en vaak simpelweg wordt platgeslagen in het hebben van een manische of depressieve toestand. Bovendien hebben we de temporele dynamiek tussen de vijf symptoomdimensies geanalyseerd. Symptomen van de dimensie 'lusteloosheid' vertoonden de hoogste 'out-strength' en de veranderingen ervan gingen vooraf aan die van 'somatisch/suïcidaliteit', terwijl veranderingen in 'kern (hypo)manie' voorafgingen aan die van 'dysfore manie'. Zo lijkt een toestand van 'lusteloosheid' te volgen op een toestand van 'somatisch/suïcidaliteit', of andersom, waarbij verbeteringen in 'lusteloosheid' gevolgd werden door verbeteringen in het domein van 'somatisch/suïcidaliteit'. Op dezelfde manier leken afnames en toenames in het domein 'dysfore manie' gevolgd te worden door vergelijkbare veranderingen in het domein 'dysfore manie'.

Naast affectieve symptomen kunnen patiënten met BS cognitieve beperkingen en tekorten in emotieregulatie vertonen tijdens episoden en ook tijdens euthymie. In **hoofdstuk 6** hebben we een meta-analyse uitgevoerd van fMRI-studies bij patiënten met BS, waarbij we emotieverwerking, beloningsverwerking en werkgeheugen hebben onderzocht, domeinen die allemaal afhankelijk zijn van de juiste activiteit in het fronto-limbische netwerk. Dit netwerk bestaat uit twee delen: het frontale gedeelte, dat voornamelijk bekend staat om zijn denkfuncties, en het limbische gedeelte, dat vooral betrokken is bij emoties. Het omvat onder andere de prefrontale cortex (PFC), amygdala, anterior cingulate cortex (ACC), hippocampus en nucleus accumbens. Deze gebieden werken samen om emotionele prikkels te verwerken, emotionele reacties te genereren en te reguleren, en een rol te spelen in het geheugen en motivatie. Het fronto-limbische netwerk speelt een cruciale rol bij het functioneren van individuen en kan verstoord zijn bij bepaalde psychische aandoeningen, waaronder bipolaire stoornis. Onze bevindingen toonden significante verschillen in hersenactiviteit bij patiënten met BS in vergelijking met gezonde controlepersonen, voornamelijk binnen het fronto-limbische netwerk. Mensen met BS vertoonden meer actieve amygdala en hippocampus en minder actieve inferieure frontale gyrus in vergelijking met gezonde mensen tijdens het verwerken van emoties. De amygdala speelt een essentiële rol bij het verwerken en reguleren van emoties. De amygdala is betrokken bij het herkennen en interpreteren van emotionele prikkels, zoals angst, woede, plezier en verdriet. De hippocampus speelt naast geheugen ook een rol bij het omgaan met sociale en emotionele situaties en het ervaren van verschillende emotionele toestanden. De inferieure frontale gyrus speelt een belangrijke rol bij de regulatie van emoties. Deze is betrokken bij het beheersen en moduleren van emotionele reacties. Het helpt bij het reguleren van de intensiteit van emoties, het onderdrukken van ongewenste emoties en het aanpassen van emotionele reacties aan verschillende situaties. De inferieure frontale gyrus werkt samen met andere hersengebieden, zoals de amygdala, om de emotionele respons te reguleren en emotionele prikkels te interpreteren. Het lijkt erop dat mensen met BS overdreven gevoelig reageren op situaties door een overactieve amygdala en een onderactieve inferieure frontale gyrus. De inferieure frontale gyrus slaagt er niet in deze reacties voldoende te onderdrukken, wat kan leiden tot problemen met emotieregulatie.

In het domein van het beloningssysteem werd een overactivatie in de orbitofrontale cortex gevonden tijdens beloningsverwerking. De orbitofrontale cortex is als het ware het beloningscentrum van onze hersenen. Een overactivatie van dit gebied bij individuen met een BS betekent dus dat ze extreem gevoelig reageren op beloningen en mogelijk moeite hebben om bepaalde impulsen onder controle te houden (vooral tijdens een manische episode).

Tijdens werkgeheugen taken vonden we een verhoogde activiteit vooral in de frontale gebieden (de ventromediale prefrontale cortex en de subgenuele anterior cingulate cortex. Beide brein gebieden zijn belangrijk als het gaat om het combineren van denkwerk en emoties.

Wij hebben ook gekeken hoe het brein van mensen met BS functioneert tijdens verschillende gemoedstoestanden (depressie, manie en stabiel). Tijdens de "stabiele" periodes van BS, ook wel euthymie genoemd, zagen we dat het limbische gedeelte van de hersenen extra actief was als het ging om emoties en beloningen. Maar als mensen met BS last hadden van manie of depressie, zagen we juist problemen in het frontale gedeelte van de hersenen.

Onze resultaten hebben laten zien dat er problemen zijn met de activiteit in belangrijke hersengebieden die te maken hebben met denken en emoties bij mensen met BS. De meeste van die gebieden maken deel uit van een fronto-limbisch netwerk. Onze bevindingen suggereren dat deze problemen met de hersenactiviteit, zowel tijdens stabiele periodes als wanneer de symptomen opspelen (depressie of manie), kunnen leiden tot problemen met het denken en de emoties bij mensen met BS.

In het kort, hebben we in dit proefschrift BS vanuit verschillende invalshoeken onderzocht. Door voorspellers en de onderlinge verbinding van symptomen in BS in de loop van de tijd te bestuderen, hebben we onze kennis uitgebreid over het herkennen van risicofactoren, het voorkomen van de conversie naar manie, vroege waarschuwingssymptomen van decompensatie en potentieel beter gerichte interventies. Door de hersenfunctie van BS te onderzoeken, hebben we meer inzicht gekregen in veranderingen in hersenactiviteitspa-tronen, die kunnen helpen bij een beter begrip van de onderliggende mechanismen van stemmingsregulatie en cognitieve tekortkomingen bij BS.

Samenvattend hebben we met dit proefschrift de volgende onderzoeksvragen proberen te beantwoorden:

Wat zijn endogene en exogene voorspellers voor de ontwikkeling en het verloop van BS?
Antwoord: We hebben aangetoond dat persoonlijkheidskenmerken zoals lage meegaandheid en boosheid endogene voorspellers zijn voor de overgang naar BS, en COVID-19 als exogene voorspeller fungeerde als een trigger voor (hypo)manische symptomen bij BS.

Hoe zijn de symptomen van BS met elkaar verbonden en hoe interageren ze in de loop van de tijd?
Antwoord: We hebben interacties en relatieve veranderingen in de ernst van symptomen bij patiënten met BS onderzocht en aangetoond dat symptomen elkaar beïnvloeden en met elkaar interageren. Op individueel niveau hebben we laten zien hoe heterogeen deze symptoomprofielen zijn, en op groepsniveau hebben we aangetoond hoe vijf dimensies in de loop van de tijd met elkaar interacteren.

Vertonen patiënten met BS afwijkende hersenactiviteitspatronen in vergelijking met gezonde controlepersonen?
Antwoord: We hebben aangetoond dat patiënten met BS, een afwijkende hersenactiviteit vertoonden in het fronto-limbische netwerk, zowel bij euthyme als symptomatische patiënten.

Met dit proefschrift dragen we bij aan de kleine onderzoeksstappen die nodig zijn om de etiologie, symptomatologie en neurobiologie van BS beter te begrijpen, met als ultiem doel bij te dragen aan betere diagnostiek en gepersonaliseerde behandeling van patiënten met BS.

Curricum Vitae

Raheleh Mesbah was born on April 14, 1981, in Karaj, Iran. At the age of 11, she and her family relocated to the Netherlands, where she began her secondary education in Wageningen. She successfully completed her high school education at the Wagenings Lyceum in the year 2000. Following her high school graduation, she returned to Karaj for a year, taking the opportunity to explore her home country. In 2001, she came back to the Netherlands and pursued a bachelor's degree in Industrial Product Design at the Applied University of The Hague. After completing her bachelor's degree, she continued her academic journey by enrolling in a master's program at TU Delft. Simultaneously, her curiosity led her to commence her first year of Psychology studies at Leiden University. Her passion for psychology grew, leading her to commit to this field. She subsequently completed her research master's in Clinical and Health Psychology alongside the Clinical Master's program. During this period, she worked part-time in healthcare, serving various populations, including the elderly, youth, and individuals with disabilities. Additionally, she took on the role of a research assistant at Leiden University.

Following her graduation, she began her career as a psychologist at the PsyQ department specializing in mood disorders in The Hague. Later, she transitioned to the Rotterdam department, focusing on bipolar disorders, where she played a coordinating role in establishing treatment group therapies. In 2016, she took on a research assistant role, alongside her clinical work, and contributed to the development of the BINCO project. In 2017 she started to combine her clinical work with her PhD in the Psychiatry department at the Leiden University Medical Centre. Her research focused on predictors, disease course, and symptomology in bipolar disorder, as well as exploring the neural mechanisms underlying bipolar disorders. In January 2023, while finalizing her thesis, she joined the PsyQ Zoetermeer Home team, further advancing her career in the field of psychology. In September of the same year, she founded her own company, "I-Rise Therapy," dedicated to delivering online psychological services.

List of publications

Mesbah, R., Koenders, M. A., van der Wee, N. J. A., Giltay, E. J., van Hemert, A. M., & de Leeuw, M. (2023). Association Between the Fronto-Limbic Network and Cognitive and Emotional Functioning in Individuals With Bipolar Disorder: A Systematic Review and Meta-analysis. JAMA Psychiatry, 80(5), 432-440.

Mesbah, R., Koenders, M., Spijker, A. T., de Leeuw, M., van Hemert, A. M., & Giltay, E. J. (2023). Dynamic time warp analysis of individual symptom trajectories in patients with bipolar disorder. Bipolar Disorders, 66(S1), S578-S579.

Mesbah, R., de Bles, N., Rius-Ottenheim, N., van der Does, A. J. W., Penninx, B. W. J. H., van Hemert, A. M., de Leeuw, M., Giltay, E. J., & Koenders, M. (2021). Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder. Depression and Anxiety, 38(6), 671-681.

Koenders, M.*, **Mesbah, R.***, Spijker, A., Boere, E., de Leeuw, M., van Hemert, B., & Giltay, E. (2021). Effects of the COVID-19 pandemic in a preexisting longitudinal study of patients with recently diagnosed bipolar disorder: Indications for increases in manic symptoms. Brain and Behavior, 11(11), e2326.
shared first authorship

Mesbah, R., Koenders, M. A., Spijker, A. T., de Leeuw, M., Boschloo, L., Penninx, B. W. J. H., van Hemert, A. M., & Giltay, E. J. (2019). Personality traits and the risk of incident (hypo)mania among subjects initially suffering from depressive and anxiety disorders in a 9-year cohort study. Journal of Affective Disorders, 259, 451-457.

Riedinger, A.M., **Mesbah, R.**, Koenders, M., Henderickx, J.G.E., Smits, W.K., Filali, E. El., Geleijnse, J.M., van der Wee, N.J.A., de Leeuw, M., Giltay E.J. A healthy dietary pattern is associated with microbiota diversity in recently diagnosed bipolar patients: the Bipolar Netherlands Cohort (BINCO) study. Journal of Affective Disorders, (under review)

Hagenaars, M. A., **Mesbah, R.**, & Cremers, H. (2015). Mental Imagery Affects Subsequent Automatic Defense Responses. In Frontiers in Psychiatry (Vol. 6). https://doi.org/10.3389/fpsyt.2015.00073

Stoffels, M., Nijs, M., Spinhoven, P., **Mesbah, R.**, & Hagenaars, M. A. (2017). Emotion avoidance and fear bradycardia in patients with borderline personality disorder and healthy controls. Journal of Behavior Therapy and Experimental Psychiatry, 57, 6-13.

Acknowledgements

This journey has been marked by challenges and triumphs, and I am deeply indebted to those who have walked beside me.

My promotor: Bert van Hemert. I express my deepest gratitude for affording me this opportunity and placing your trust in me. Your philosophical insights alongside the critical and constructive feedback, guidance, support, and understanding during challenging moments have been a pillar of strength for me.

My co-promotors: Erik Giltay and Manja Koenders. I feel grateful and honored to have con-ducted my research under your supervision. Erik, your knowledge across diverse fields, efficiency, and research enthusiasm, coupled with your guidance, support, and sense of humor, made this journey not only possible but incredibly enjoyable for me. Manja, I am grateful for your trust, guidance, and openness. I'm impressed by how you bring a thoughtful perspective, insight, and positive energy.

I extend my gratitude to Max de Leeuw and Nic van der Wee for your valuable supervision. I'm thankful for your guidance and belief in my abilities, which played a crucial role in yielding outstanding results. Max, thank you for your step-by-step guidance and encouragement to strive for excellence.

My sincere thanks to my LUMC colleagues. Gea and Mirjam, thank you for your support and confidence in me. Nathaly, Mirjam, Alice, Lisanne, Margot, Rebecca, Misha, Petra, Christa, Wilma, Erwin, Floor, and Ikram, thanks for the pleasant collaboration and support.

I'm thankful to my amazing office mates, Nienke; thank you for your support, empathy, and meaningful conversations. Your presence as my paranymph is an honour. Ericka, your calming smile brought positivity to me. Stephanie, your positive energy and humor have been uplifting. To Wessel and David, thank you for the joyful moments.

I am also grateful to my colleagues of PsyQ especially Elvira, Amati, Stefanie, Renate, Anne-Marie, Anna, Ellen, and Petra, for fostering a conducive work environment, enabling me to learn from them while sharing moments of laughter and connection.

Annet, how grateful I am to have encountered you during the completion of my master's as a university lecturer. Thank you for your trust in my potential and guidance throughout my journey.

My best friends, Soheyla, Samira, Assal, and Sarah thank you for decades of friendship, support, laughs, and tears we shared together. Your faith in me and encouragement to persevere has been instrumental in helping me reach this milestone. My dear friends Payman, Samrad, Sadaf, Jos, Kaweh, Siamak, Bas, Celine, Paulina, Bart, Benjamin, Behnam, Nima and Ada. Thanks for the beautiful memories.

I am deeply grateful to Floor and Huib; you treated me like family and provided endless support. I'm grateful to Iris, Roos, Rob, and Oma Jeane for welcoming me into your family circle and years of support.

I'm grateful to my parents-in-law for providing support and care. Your help in raising Adrian and being the best grandparents to him is truly appreciated. Dear Hesam, Maryam, and Aryan thank you for your warmth, encouragement and the enjoyable moments.

I am grateful for my family, whose support I have always felt despite the physical distance. Ali and Negin, you have been a constant pillar, standing by my side and providing support throughout the years. I truly cherish the strong bond we share. Ali, Thanks for being an amazing brother. I admire and look up to you in many ways. Sepideh and Shahin, I am grateful for your constant presence and support. I cannot thank you enough for being there for and helping me in every possible aspect, including assisting me in raising Adrian. Sepideh, not only are you an incredible sister, but you also serve as my confidant and personal psychologist. Dear Baba Maman, I am deeply grateful for your unconditional love and support. As exceptional role models, you have emphasized the importance of confronting challenges with bravery. Thank you for always having faith in me, even when I was just 16, and your choice to allow me to pursue what was best for me.

To my little angels, Ilya, Kian, Ryan, Daniel, Danica, and Armin, thank you for your energizing cuddles and presence.

I'm deeply blessed with the sunshine of my life Adrian, you make me feel alive! Thank you for recharging my batteries. As I always say to you "endlessly to the sun and back" and I'm always proud of you. Cyba, you were literally always by my side, and I deeply miss your innocent presence. Parham, thank you for your endless support, love, and for being a great technical and scientific sparring partner. You're my soulmate; we've grown up together, and I hope to grow old with you. Having you consistently by my side is an extraordinary blessing, and I treasure every moment of our life together.