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Predictors, symptom dynamics and neural mechanisms of bipolar disorders

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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).

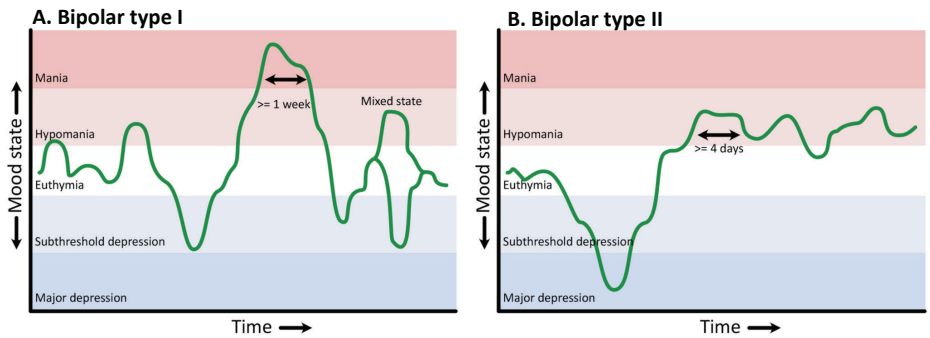

Figure 1.1: Differentiation between bipolar disorder type I (A) and II (B).

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.

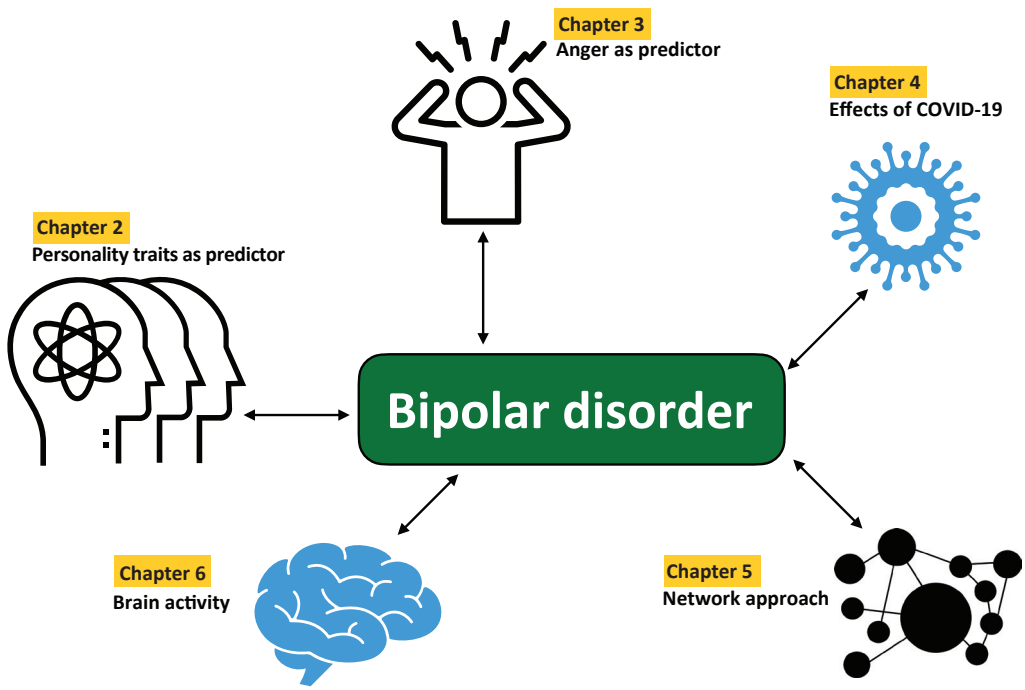

Figure 1.2: Schematic representation of chapter content.

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.