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Predictors, symptom dynamics and neural mechanisms of bipolar disorders

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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.