## Balancing the highs and lows

Orhan, Melis Miene

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# BALANCING THE HIGHS AND LOWS

## Diagnostics, understanding, and treatment of recurrence in older adults with bipolar disorder

Amsterdam UMC
Universitair Medische Centra
Department of Psychiatry

**Melis Orhan**

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Melis Miene Orhan

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# BALANCING THE HIGHS AND LOWS

## Diagnostics, understanding, and treatment of recurrence in older adults with bipolar disorder

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and here you are living,
despite it all

- rupi kaur

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# CHAPTER 1

# General introduction

**Text box 1:** Case study, "Mrs. M".

In 2016, Mrs. M. was referred to the old age psychiatry outpatient clinic by her general practitioner. At the time of the intake, she reports that she has been experiencing 'energetic periods' in which she has trouble with sleeping, irritable mood, fast thoughts, planning a lot of new activities and an increased urge to speak. These periods often occur once per two years and lasts for about three months. They alternate with depressive and euthymic episodes. During depressed episodes, she experiences a lowered mood, anxiety and a lack of energy. However, up until now she has not received therapy, because they never brought her into "real" trouble, so she reports. She has the feeling that these periods arise and disappear out of nowhere. After the intake, it was concluded that Mrs. M. was suffering from bipolar disorder (BD), type II. Pharmacotherapy was advised, starting with lithium, and she also participated in IPT-SRT group therapy. Besides experiencing affective symptoms, she also experiences difficulties in other areas of functioning. Mrs. M. has a partner with whom she used to live together, but due to conflicts between them, they decided to live apart. This is hard for Mrs. M., since she experiences anxiety whenever she is spending time alone. After the intake, she started with lithium use, and has gained 25 kg. Also, as a side-effect, she experiences a lot of tremors that limit her mobility. In addition, she repeatedly reports to feel a bit numb due to the medication. Mrs. M. has cardiac arrhythmias, COPD and therefore often experiences shortness of breath. Since 2019, she experiences cognitive problems, especially problems with her short-term memory. Appointments are sometimes hard for her to memorize. She used to read a lot, but she doesn't do this anymore because she can't remember what she just read. Conversations with multiple persons are hard for her, she then withdraws from the conversation. She has become insecure in driving her car; therefore, she doesn't do this anymore since the last 2-3 years. After the COVID-19 outbreak in March 2020, she started to experience more mood symptoms and started worrying about her health. Due to the measures, she was not able to keep her daily routines. in June 2020 she was hospitalized in a psychiatric hospital. Afterwards, in July 2020, she experienced a somatic hospitalization after a cardiac insult. In October 2020, she was again somatically hospitalized whereas she got COVID-19 and had a pulmonary embolism and got delirious afterwards. After these psychiatric and somatic hospitalizations, she felt more and more dependent to her partner, causing more difficulties between them. Therefore, they participated in the partner-relationship group therapy in 2021.

The above-described case of Mrs. M. in text box 1 illustrates the versatility of bipolar disorder (BD) and the different areas that can be affected by the disorder. BD is a chronic psychiatric disorder, characterized by recurrent depressive episodes as well as manic, hypomanic or mixed episodes[1]. BD is classified as a lifelong, recurrent condition, associated with functional decline and a reduction in quality of life[2,3]. It is regarded as

highly disabling, where it has been ranked as the 17th leading source of disability among all diseases worldwide[4]. Many patients with BD experience residual mood symptoms, social dysfunction, and cognitive impairments[5] with negative consequences for daily functioning. Although the prevalence of BD seems to decline with age, still 8-10% of psychiatric inpatients over age 55-60 are diagnosed with BD[6] and a quarter of all patients with BD is over the age of 60[7]. It is expected that in the near future, the number of older adults with BD (OABD) will increase to over 50% due to increased life expectancy and to changing population demographics (i.e. increasing proportion of older adults)[8]. OABD, defined for BD patients over the age of 50[7] represents approximately 25% of the BD population. The OABD population shows differences in clinical appearance, cognitive patterns and psychosocial functioning when compared to younger BD patients. This stresses the recommendation to consider this group as a specific population, thereby warranting specific approaches and treatment strategies. However, up until this moment knowledge in these areas is lacking.

The aim of this dissertation is to improve the knowledge about OABD by gaining insight into the diagnostic aspects, increasing the understanding of the clinical phenotype and its mutual associations and investigate treatment strategies in OABD. We will test the ability to use different measurements in order to assess the severity of OABD, by indicating depressive symptoms, psychosocial functioning and cognitive functioning. In order to gain a better understanding of OABD, we will focus on the associations between cognitive, social and psychological functioning in OABD. Subsequently, we will explore new treatment strategies by testing the feasibility and acceptability of two different pilot studies in this group. Finally, a general outline of this thesis is provided.

## Bipolar disorder

BD is characterized by episodes of depression, mania, hypomania and episodes with mixed features/mixed episodes in alternation with periods of symptom-free periods. For a summary of the diagnostic criteria of BD[9] see Table 1. The studies in this thesis are based on DSM-IV criteria of BD. BD is specified in different types, including BD type 1, BD type II, cyclothymic disorder and other specified BD. BD I is characterized by at least one manic episode and major or less severe depressive episodes; but may be diagnosed after one manic episode only. BD II is characterized by the occurrence of one or more major depressive episodes and at least one hypomanic episode. Cyclothymic disorder is a chronic, fluctuating mood disturbance characterized by numerous hypomanic and depressive mood of which none meet the formal criteria for a full depressive or manic episode with a duration of minimal 2 years. Other specified BD is characterized by bipolar features but not meeting the criteria of any of the above-mentioned disorders, e.g. very rapid alternation (over days) between manic and depressive symptoms, recurrent hypomanic episodes without intercurrent of depressive symptoms[10,9]. The

first episode of BD is usually depressive, and for most persons with BD, depressive episodes are more prominent during the course of the illness[11]. Therefore, BD is often misdiagnosed for major depressive disorder, and in up to a third of affected persons, BD is not diagnosed until 10 years after the onset of symptoms[12].

## Older adults with bipolar disorder

Patients with OABD account for 6% of geriatric psychiatric outpatient visits and 8% - 10% of inpatient admissions[6], with an overall prevalence of late-life mania of 6% in older psychiatric inpatients[13]. Approximately 70% of patients with OABD are women, possibly because of increased survival rates for women[6]. The presentation, severity, and prevalence of manic and depressive symptoms in OABD differ little from adults younger than 60 years of age[14,15] and no differences were found between early-onset and late-onset subtypes[6]. The evolution of bipolar disorder symptoms and functioning across the lifespan is incompletely understood. Some studies suggest a worsening of symptoms over the course of BD, with more depressive symptoms in OABD and less psychotic symptoms[13,15].

Long-term outcomes of BD are associated with cognitive deficits[16,17], impaired psychosocial functioning, and increased risk of dementia and premature death[18]. The underlying causes of this poor prognosis include lifestyle choices, concurrent comorbidities, psychosocial adversity, and suboptimal access to health care[18]. There is evidence that suggests that BD in later life may become more complex, with poorer cognitive functioning compared to non-clinical older adults[19]. These differences between OABD and younger adult BD patients, warrants reevaluation of diagnostic instruments, knowledge of disease mechanisms and treatment strategies whereas these are mostly developed for the younger adult BD patient population.

## Diagnostics and assessment

Difficulties and delay in the diagnosis of BD impede effective treatment, and amplify the burden of illness on the individual, family and society[20]. Therefore, early detection and intervention is regarded as crucial to improve long term outcome in BD[21,22,23,24]. The prevalence of misdiagnosis of BD is high in general, ranging from 48% to 69%[12]. However, diagnosing affective symptoms in older adults can be difficult. Most diagnostic criteria and assessment instruments, such as the International Classification of Diseases (ICD-10[25]) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5[9]) are developed and validated in younger adult patient groups, and have limited applicability for the older patient population in both research and clinical practice. Besides taking into account psychiatric symptoms, as described earlier, in order to make an estimation about the current state and wellbeing of the individual, other aspects of the disorder need to be taken into account.

**Table 1:** Diagnostic criteria for mood episodes according to DSM-5[9].

| **Core symptom: Major depressive episode**<br>A period of at least 2 weeks with at least one core feature and four associated features and cause significant distress or impairment in social, occupational, or other important areas of functioning. | |
|---|---|
| **Core feature** | **Associated features** |
| Depressed mood | Change in appetite or weight |
| Loss of interest or pleasure in nearly all activities | Insomnia or hyposomnia |
| | Psychomotor retardation or agitation |
| | Fatigue or loss of energy |
| | Feelings of worthlessness or guilt |
| | Difficulties in thinking, concentrating or making decisions |
| | Recurrent thoughts of death, suicidal ideation |
| **Core symptom: Manic episode**<br>A period of abnormal mood (core feature) including 3 or 4 (in case of irritable mood) associated features that lasts at least one week or less if hospitalization is required. The disturbance must be sufficiently severe to cause impairment in social, occupational or other important areas of functioning or by the presence of psychotic features. | |
| **Core feature** | **Associated features** |
| Abnormally and persistently elevated, expansive or irritable mood | Inflated self-esteem or grandiosity |
| | Decreased need for sleep |
| | Pressure of speech |
| | Flight of ideas |
| | Distractibility |
| | Increased involvement in goal-directed activity or psychomotor agitation |
| | Involvement in activities with painful consequences |
| **Hypomanic episode**<br>Core and associated features as in manic episode with a duration of at least 4 days. The symptoms are associated with a change in normal functioning, but do not cause marked impairment in social or occupational functioning. | |

* For all episodes the additional requirement must be fulfilled that the symptoms are not due to the direct physiological effects of a substance (abuse of drugs or medication) or a general medical condition.

An important aspect in diagnosing one's current state as psychiatric or pathological, is their current level of functioning. Traditionally, it was assumed that BD patients are often asymptomatic between episodes, and return to normal functioning after each episode. However, more recent studies have shown a less optimistic picture[26], with many patients in clinical remission experiencing residual mood symptoms, social dysfunction, cognitive impairment and stigma[27]. And as a result, 30-60% of adult patients with BD suffer from poor psychosocial functioning after clinical remission of symptoms[28], with this percentage is estimated to be even higher in OABD as older age has been related to lower psychosocial functioning in BD[29]. When compared to younger adult BD patients,

OABD are even more frequently characterized by progressive cognitive and overall functional impairment[30,31]. In addition, somatic comorbidities are frequent in OABD, with an average of 3 to 4 comorbid medical conditions[32]. This burden of poor somatic health is reported to further increase with age in OABD[33], which may further decrease functioning in this group. Therefore, mood symptoms and current level of functioning must be continuously reevaluated when treating OABD patients.

## Understanding disease mechanisms

OABD is a complex and disabling disorder, but the clinical course is understudied in this group[34]. Some studies suggest there is an increasing risk of recurrence after every new episode[35], especially among older patients[36], but with less frequent hospitalizations[37]. Recurrent mood episodes remain a major challenge for patients with BD, with a median time to a subsequent mood episode after the index episode of 1.4 years and highest risk in patients with persisting subsyndromal symptoms[38]. The neuroprogression hypothesis postulates that every mood episode is toxic to the brain and leads to cognitive decline in BD[39]. Studies in younger adult BD patients show that a greater neurotoxicity effect is produced by manic episodes[40]. It is therefore of great importance to gain more insight in factors associated with recurrence in OABD. The first step in preventing recurrence in this group, is to understand different disease aspects that affect the clinical course in OABD and their mutual interactions.

A first aspect of interest is social functioning. Social functioning is a multifactorial concept, in which several associated factors impact each other. Changes associated with ageing may have a negative influence on social functioning, like physical dependence and reduction of social network size. Also positive factors can compensate, like adaptive coping styles and availability of support[41,42]. Social functioning seems to fluctuate in parallel with changes in mood symptom severity[43], indicating that more severe depressive or manic symptoms lead to more social dysfunction[44] and it interacts with other aspects of functioning, for instance cognitive functioning[45].

Another aspect of interest is cognitive functioning. Cognitive functioning is important for our daily living. Intact cognitive abilities are needed for planning activities, remembering important things, focusing attention to strenuous efforts and shifting between different tasks[46]. OABD often exhibit greater cognitive impairment compared with healthy peers, even between mood episodes[47]. Despite cognitive dysfunction being widely considered to be a core feature of BD, there is a lack of specific knowledge about cognitive performance in OABD. Cognitive dysfunction is prevalent in more than half of individuals with OABD, as compared with healthy controls (HC)[48]. A meta-analysis conducted in OABD revealed poor performance in episodic memory, attention, information processing speed, verbal fluency, and some domains of the executive

functions as compared with HC. It is also known to be related to the clinical course in adult BD, with worse cognitive functioning being associated with a higher number of mood episodes, longer illness duration and more psychiatric admissions[49].

## Treatment strategies

In order to prevent recurrence and decrease current mood symptoms, the use of appropriate treatment strategies is essential. Unfortunately, the impact of living with BD in older adulthood has received far less attention than the adult population and as a result, most guidelines lack specific recommendations for OABD[50] and treatment strategies are mostly extrapolated from studies conducted in the younger adult BD population. In general, treatment of OABD can be more complex than in younger patients and faces different needs given the higher prevalence of somatic comorbidities, sensitivity to treatment-related adverse effects, and complex psychosocial challenges[7]. It was shown that the care needs of older psychiatric patients were better attended to by specialized old age psychiatry teams compared with generalized psychiatric teams[51], indicating that strategies that are successful in younger adults cannot be extrapolated to the older patients[52].

Until now, the focus of treatment in BD is mostly focused on decreasing mood symptoms by means of pharmacotherapy. Several clinical features are different in OABD when compared to younger adults with BD, thereby creating challenges in this group. For instance, altered cellular functions frequently require adaptation using lower doses in the older adults and adverse drug reactions increase with age, even at lower drug concentrations. In addition, an elevated probability of drug interactions exists given the larger number of medications taken, and an increased number of medications may also cause difficulties with adherence, especially in those with cognitive impairment[53,54]. There is increasing recognition that pharmacotherapy alone cannot prevent recurrence of mood episodes or fully alleviate post-episode symptoms of functional impairment[55]. In addition, pharmacological treatments have been shown to contribute to somatic comorbidity, illness burden and treatment non-adherence[56] and are often less preferred by patients with mood symptoms[57].

Many BD patients experience recurrent mood episodes even despite the use of medication. As described earlier, BD is characterized by a high degree of psychosocial impairment, low rates of medication adherence, interpersonal dysfunction and cognitive impairment. Each of these domains is reasonably addressed by psychotherapeutic interventions, especially when delivered in combination with pharmacotherapy. Psychotherapy, when provided at all, is often viewed as an adjunctive treatment[58]. Evidence from RCT's indicates that combining pharmacotherapy with psychotherapy, including cognitive behavioral therapy (CBT), family-focused therapy, interpersonal

and social rhythm therapy (IPSRT), and group psycho-education, is more effective than pharmacotherapy alone in stabilizing symptoms and reducing recurrences among BD outpatients[55,59,60]. A recent systematic review and meta-analysis showed that psychotherapy has a significant added value in different phases in the treatment of BD. When the treatment goals center on prevention of recurrences, patients could profit from family or group psychoeducation with guided skills training and active tasks to enhance coping skills. When the immediate goal is recovery from moderately severe depressive or manic symptoms, cognitive restructuring, regulating daily rhythms, and communication training may be associated with stabilization[61]. However, all these mentioned types of psychotherapy lack evidence for the application in the older patient population.

## COVID-19

As of the beginning of 2020, the coronavirus disease 19 (COVID-19) has had an overwhelming impact on the lives of people around the world. As of March 17th, 2020, the Dutch government has introduced measured aimed at reducing the spread of COVID-19 in line with the World Health Organization: quarantine, social distancing and isolation of infected populations in order to contain the pandemic. These regulations may decrease social support and increase loneliness[62], and may also increase the risk of irregular social and circadian rhythms. The burden seems particularly relevant to vulnerable populations, such as people with mental disorders and older adults. The course of COVID-19 is more serious and potentially fatal in older adults compared to younger adults and in those with somatic diseases, therefore these groups are considered "at risk." Studies conducted during this period revealed that BD participants reported worse cognitive symptoms when compared to healthy controls[63], more elevated pandemic-related stress, sleep difficulties, and anxiety[64]. In BD participants, more social restrictions were associated with greater psychological distress[65]. It is clear that OABD patients are at risk for COVID-19 in terms of age, but also in terms of their mental health. However, it remains unclear how this pandemic affects this group.

## Aims of this thesis

The general aims of this thesis are:

- To expand our knowledge on the diagnostics in OABD,
- To create a greater understanding of clinical phenotype and its mutual interactions in OABD
- To assess the feasibility and acceptability of new treatment approaches in OABD

The ultimate goal is to prevent recurrence where possible, and treat current mood symptoms in order to obtain an optimal level of wellbeing in this group.

## Studies used in this thesis

### *The Dutch Older Bipolars (DOBi) cohort*

DOBi is a dynamic cohort study focusing on clinical and functional characteristics in older adults with BD. The initial sample was included in 2012 (aged 60 and over). Participants were included in follow-up measurements in 2015. In 2017, a new wave of participants (aged 50 and over) was included in the cohort. These participants were included in 2020 for follow-up measurements. In total, 227 OABD patients were included in the baseline sample. At the time of inclusion, all patients received treatment at GGZ inGeest in Amsterdam, an outpatient mental health facility. Chapters 3, 4, 5, and 6 are based on DOBi data.

During the COVID-19 pandemic, 83 participants included in the baseline sample were also included in subsequent DOBI-COVID-19 measurements in 2020, focused on COVID-related factors. Chapters 7 and 8 are based on DOBI-COVID-19 data.

### *The Netherlands Study of Depression in Older adults (NESDO)*

NESDO is a multi-site cohort study of 378 depressed and 132 non-depressed older adults aged 60 – 93[66]. In 2010, depressed older adults with recruited from both mental health care institutes and general practices. Non-depressed older adults were recruited from general practices. Participants were again interviewed after 2 years and 4 years. For this thesis, data from the baseline measurement was used. In chapter 4, NESDO-data are used to compare cognitive functioning in late life depression with cognitive functioning in OABD.

### *The Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD)*

The GAGE-BD database is a large integrated sample comprising archival studies being used to advance understanding of OABD[34]. The GAGE-BD dataset is a multi-national research initiative and pools archival research and clinical datasets to provide an evidence platform for OABD (aged 50 years and over). As of May 14th, 2021, 20 different studies have contributed data on 1519 men and women with OABD. Chapter 2 is based on wave 1 GAGE-BD data.

## OUTLINE

In part I, the challenges and pitfalls of assessing mood symptoms and daily functioning in OABD are investigated:

- **Chapter 2** presents a comparison of different depression severity measures in OABD. By using a large integrated international dataset, this study aimed to illustrate the added value of harmonizing datasets and investigated whether harmonization led to a loss of statistical power or if it was an effective strategy to create larger sample sizes.
- **Chapter 3** provides an investigation of the psychometric qualities of the Functioning Assessment Short Test for Older adults (FAST-O). Whereas there is a lack of easy-to-use instruments in order to indicate functioning in this group, this study aimed to explore the reliability and validity of the FAST-O in an OABD population.
- In **Chapter 4** we will focus on cognitive functioning in OABD and comparing this to cognitive functioning in late life depression and healthy controls. The aim of this study was to investigate whether cognitive dysfunction in these groups can be explained by the current depressive symptoms.

In part II, the clinical phenotype of OABD is investigated:

- **Chapter 5** focuses on the relationship between cognitive and social functioning in OABD.
- **Chapter 6** aims to investigate social, psychological and cognitive factors that might be related to the clinical course in OABD.
- In **Chapter 7**, psychiatric symptoms are studied during the COVID-19 pandemic in OABD and aimed to explore differences between symptomatic and euthymic patients.
- **Chapter 8** aimed to study the course of depressive, manic and anxiety symptoms in OABD patients during the first 6 months of the COVID-19 pandemic. The interaction between loneliness, mastery and psychiatric symptoms was explored during the first 6 months of the COVID-19 pandemic.

In part III, we will focus on possible treatment strategies for OABD.

- **Chapter 9** presents the feasibility and satisfaction of a pilot study for mild cognitive impairment in OABD: "Brain Train".
- **Chapter 10** presents the feasibility and effectiveness of a pilot study of group interpersonal social rhythm therapy (IPSRT) for recurrent mood disorders.
- Finally, **Chapter 11** provides a summary of all above noted chapters followed by a general discussion, clinical implications and suggestions for future research.

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1

# **PART I:** DIAGNOSTICS

# CHAPTER 2

# Comparing continuous and harmonized measures of depression severity in older adults with bipolar disorder: Relationship to functioning

Melis Orhan, Caitlin Millett, Federica Klaus, Hilary P. Blumberg, Farren Briggs, Kuo-Hsuan Chung, Nicole Korten, Kaitlin McManus, Patricia van Oppen, Regan E. Patrick, Kaylee Sarna, Ashley Sutherland, Shang-ying Tsai, Luca M. Villa, Joy Yala, Martha Sajatovic, Katherine E Burdick, Lisa Eyler, Annemiek Dols & the GAGE-BD consortium

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## ABSTRACT

**Background:** Harmonizing different depression severity scales often requires creation of categorical variables that may decrease the sensitivity of the measure. Our aim was to compare the associations between categorical and continuous and harmonized measures of depression and global functioning in a large dataset of older age patients with bipolar disorder (OABD).

**Methods:** In the Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) the 17-item Hamilton Depression scale (HAM-D), Montgomery Asberg Depression Rating Scale (MADRS) or the Center for Epidemiological Studies Depression scales (CES-D) was used to assess current depressive symptoms, while the Global Assessment of Functioning (GAF) assessed functional status. Data were harmonized from 8 OABD studies (n = 582). In each subsample, the relationship of depression severity as a continuous and categorical measure was compared to GAF. In the total sample, harmonized ordinal depression categories were compared to GAF.

**Results:** Effect size and variance explained by the model for the categorical measure in the total sample was higher than both the categorical and continuous measure in the CES-D subsample, higher than the categorical but lower than the continuous measure in the HAM-D subsample, and lower than both the categorical and continuous measures in the MADRS subsample.

**Discussion:** Associations were only slightly larger for the continuous vs. categorical measures of depression scales. Harmonizing different depression scales into ordinal categories for analyses is feasible without losing statistical power.

# INTRODUCTION

Bipolar disorder (BD) is a severe, often lifelong mood disorder defined by alternating elevated periods of mania (BD 1) or hypomania (BD 2), although individuals tend to spend the most time in depressive episodes[1]. Although the prevalence of BD seems to decline with age, roughly 25% of all patients with BD are 60 years or older[2]. Older patients with BD are particularly vulnerable to functional impairment, but research on this topic is relatively sparse and the presentation of the illness in later life is incompletely understood[3]. Most studies in older age BD (OABD) have been conducted in small samples, with most clinical research studies in OABD studying fewer than 50 patients[3] and therefore lacking statistical power. A potential strategy to overcome the challenge of interpreting findings from existing studies is to pool or integrate data from these already existing studies (i.e., harmonize). Harmonizing can be used to describe the procedure of placing variables on the same scale in order to permit pooling of data from many studies[4,5]. Harmonizing existing datasets will lead to greater sample sizes and more statistical power—making it a necessary tool for research. Importantly, harmonizing disparate datasets is essential to create large enough study samples to answer core research questions in OABD, particularly related to everyday functioning.

Considering the relative chronicity of BD, impaired daily functioning is regarded as a central aspect of the disease[6], but data on functional impairment in OABD is relatively sparse. Recent work has suggested that functioning is increasingly limited in OABD when compared with healthy older adults, due to a limited social network, reduced mobility, and impaired cognition[7,8,9]. Findings in a recent study suggest that more severe manic or depressive symptoms are associated with poorer functioning in OABD[8]. In line with this, a study conducted[10] found that more severe depression, somatic comorbidities, and impaired cognition were all associated with lower functioning in OABD. These findings support the notion that multiple aspects of BD impact patients' overall functioning, particularly acute depressive symptoms. Therefore, potential value can be found in harmonizing studies to include multiple factors and study their relationship with functioning in OABD.

Given the limitations in existing research studies, creating larger samples by combining existing studies is of great importance to answer specific research questions concerning associations between core symptoms, and to account for the great heterogeneity[6] in this group. To date, no studies have harmonized different measures of depressive symptom severity in OABD. In the Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD), contributing studies assessed depressive symptom severity using three different scales: Hamilton Depression Scale (HAM-D[11]), Montgomery Asberg Depression Scale (MADRS[12]) or the Center for Epidemiological Studies Depression Scale (CES-D[13]).

By using a large integrated international dataset of studies on OABD and the concept of global functioning to illustrate the possible added value of harmonizing different datasets, this study investigated whether harmonization led to a loss of statistical power or if it was an effective strategy to create larger sample sizes. This will be illustrated by investigating the different associations between depression scores and global functioning. In a large integrated dataset, the association between categorical symptom severity based on clinical cutoffs for each of three commonly used depression symptom rating scales will be compared with a measure of global functioning and the association between total scores in these rating scales. We hypothesized that associations between depression score and functioning would be larger for the continuous measures than categorical versions of these variables. Regardless of outcome, these analyses can provide critically important information about how to combine depression data across multiple OABD studies using different rating measures.

# METHODS

## Participants

GAGE-BD comprises pooled data from multiple archival studies made possible by an international team of investigators who have an interest in BD and aging. The overarching approach and methods of GAGE-BD have been described elsewhere[14]. The sample for this analysis was derived from 8 studies from 6 sites across the globe, reporting data on older age (> 50) individuals with BD ($n$ = 582). Studies were included when a depression measure and Global Assessment of Functioning (GAF) score (American Psychiatric Association, 2000) were available.

Included studies in this secondary analysis were the Treatment Adherence Enhancement in Bipolar Disorder (CAE, $n$ = 184), Dutch Older Bipolars cohort (DOBi1, $n$ = 78, DOBi2, $n$ = 59), Dynamic Inflammatory and Mood Predictors of Cognitive Aging in Bipolar Disorder (Inflammaging, $n$ = 66), Mood Disorders Research Program Database (Yale, $n$ = 68), Taipei Medical University (TMU, $n$ = 54), Geriatric Psychiatry Mood Disorders Research Database (GMDD, $n$ = 35), and Open-label, Prospective Trial of Lamotrigine for Symptoms of Geriatric Bipolar Depression (GERI-SAD, $n$ = 38). For an overview of the included studies, see supplemental material[8].

Three studies were included in the MADRS sample (CAE, GMDD, GERI-SAD; $n$ = 257), three studies were included in the HAM-D sample (TMU, Inflammaging, Yale; $n$ = 188), and two studies were included in the CES-D sample (DOBi1 & DOBi2; $n$ = 137). All participants gave their informed consent for participation. Approval to contribute data was obtained by local site institutional review boards or ethics committees at originating sites as

appropriate, and data use agreements were executed between each contributing site and the GAGE-BD coordinating center (Case Western Reserve University School of Medicine). Studies were performed according to the Helsinki declaration.



## Measures

### *Demographic and clinical characteristics*

Age, sex, level of education, BD type diagnosis, duration of illness, and lifetime psychiatric hospitalizations were obtained through interviews and checked in medical records. Current mania symptoms were assessed by the Young Mania Rating Scale (YMRS[15]).

### *Depression scales*

HAM-D

The Hamilton Depression Rating Scale[11] was used in three studies. "This rating scale is used to assess the severity of depressive symptoms during the last three days". This scale contains 17 variables, with variables measured on five-point or three-point scales. The latter is used where quantification of the variable is either difficult or impossible. The scale is rated by a clinician. Scores of 0-7 are considered non-depressed, 8-16 suggest mild depression, 17-23 moderate depression and scores over 24 are indicative of severe depression. The maximum score is 52 on the 17-point scale[16].

MADRS

The Montgomery-Åsberg Depression Rating Scale[12] was used in three studies. This 10-item rating scale is used to assess the severity of depression during the last week. The scale is rated by the clinician. Scores of 0-6 are considered non-depressed, scores of 7-34 indicate mild to moderate depression and scores over 34 indicate severe depression[17]. The maximum score is 60 points.

CES-D

The CES-D[13] was used in two studies. The CES-D is a self-report scale, consisting of 20 items. It measures depressive symptoms during the previous week, with scores ranging from 0 to 60. Scores 0 - 16 represent no depression, scores over 16 indicate clinically relevant depression. Scores 16-27 represent mild to moderate depression and scores over 28 represent severe depression.

### *Global functioning*

GAF

The Global Assessment Functioning Scale (GAF[18]) was used to assess the level of global functioning in all studies, as estimated by patients' treating psychiatrist. The score represents a global rating of current global functioning ranging from 1 to 100, with lower scores indicating lower functioning and scores >90 suggesting no functional

impairments. Benchmarks are based on the quality of several areas of functioning, such as personal hygiene, the quality of social contacts, and occupational functioning.

### Statistical analysis

Analyses were conducted within three subsamples based on which depression measure was utilized (HAM-D vs MADRS vs CES-D) and in the total harmonized sample. In order to harmonize depression severity across the total sample, regardless of the scale used, the continuous total scores were transformed into a three-level categorical variable (none, mild-moderate, or severe depression) that were calculated as follows: no depression (HAM-D: 0-7, MADRS: 0-6, CES-D: 0-15); mild-moderate depression (HAM-D: 8-23, MADRS: 7-34, CES-D: 16-27); and severe depression (HAM-D ≥ 24, MADRS ≥ 35, CES-D ≥ 28). We compared characteristics of subsamples using ANOVA and Tukey's Honestly Significant Difference for pairwise comparisons for continuous measures and Chi-square for discrete measures. In each subsample (those with HAM-D vs MADRS vs CES-D scores), the relationship of depression severity as a continuous measure to GAF and the categorical depression categories to GAF were compared in terms of adjusted $R^2$ for the model and effect size (partial $^2$) for depression severity, by using univariate general linear models (GLM). In each model, potential differences between contributing studies were modeled with a fixed effect of study and a depression severity x study interaction. Included covariates were age, gender and education in years. One study (GERI-SAD) had both HAM-D and MADRS scores available and was included in the MADRS sample in Table 1. This study was included in both the HAM-D and the MADRS sample for the subgroup comparison of effect sizes (Table 2), but was not duplicated in the pooled sample. In the total study sample, this study was included with MADRS data. Data and analysis code are available upon request and with appropriate institutional data use agreement. The study and analyses were not preregistered. Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 25.0, SPSS Inc., Chicago, IL).

## RESULTS

### Demographic and clinical characteristics

The demographic and clinical characteristics of the patients in the MADRS sample ($n$ = 257), the HAM-D sample ($n$ = 188), the CES-D sample ($n$ = 137) and the total sample ($n$ = 582) are summarized in Table 1. The total sample had a mean age of 57.0 ($SD$ = 12.1) and the majority were female (59.5%). The groups differed in terms of age, with the CES-D sample having the highest mean age ($M$ = 65.8, $SD$ = 7.4). The MADRS sample had the highest education in years ($M$ = 13.5, $SD$ = 2.8). The average duration of BD among the total sample was 29.4 years ($SD$ = 13.3), with an average of 4.0 lifetime psychiatric hospitalizations.

**Table 1:** The demographic and clinical characteristics of the total study sample and the MADRS, HAM-D and CES-D subsamples

| | Total sample (n = 582) | MADRS subsample (n = 257) | HAM-D subsample (n = 188) | CES-D subsample (n = 137) | Statistics $X^2$ / F (df), p-value |
|---|---|---|---|---|---|
| Age, years, M(SD) | 57.0 (12.1) | 53.1 (13.2) | 55.8 (9.8) | 65.8 (7.4) | 61.84 (3), <.01** |
| Sex, female, %(n) | 59.5 (347) | 60.3 (155) | 63.8 (120) | 51.8 (71) | 4.88 (2), .09 |
| Education in years, M(SD) | 13.1 (3.8) | 13.5 (2.8) | 12.4 (4.83) | 12.8 (3.31) | 4.69 (2), .01* |
| Occupational status, working %(n) | 23.8 (120) | 13.0 (33) | 46.6 (54) | 24.4 (33) | 49.55 (2) <.01** |
| Diagnosis, bipolar I %(n) | 65.5 (382) | 74.3 (191) | 64.4 (121) | 50.4 (69) | 167.67 (4), <.01** |
| Duration of disease in years, %(n) | 29.4 (13.3) | 24.4 (12.2) | 30.8 (12.2) | 35.3 (13.7) | 32.76 (2), <.01** |
| Age of onset, %(n) | 27.1 (14.0) | 24.5 (13.6) | 25.2 (14.0) | 30.8 (15.5) | 6.27 (2), <.01** |
| Current smoker, yes, %(n) | 37.6 (219) | 42.8 (110) | 26.1 (49) | 44.1 (60) | 209.68 (6), <.01** |
| Lifetime psychiatric hospitalizations, M(SD) | 4.0 (6.3) | 5.2 (7.6) | 4.4 (6.3) | 1.6 (1.8) | 12.45 (2), <.01** |
| GAF score, M(SD) | 61.9 (12.7) | 59.3 (10.4) | 63.6 (15.2) | 64.6 (11.9) | 10.76 (2), <.01** |
| MADRS score, M(SD) | | 18.5 (9.3) | - | - | |
| HAM-D score, M(SD) | | - | 8.6 (8.1) | - | |
| CES-D score, M(SD) | | - | - | 15.4 (9.7) | |
| YMRS score, M(SD) | 6.0 (6.0) | 7.2 (5.2) | 5.0 (6.3) | 5.0 (6.5) | 9.9 (2) <.01** |
| Depression severity (categorical), %(n) | | | | | 165.09 (4), <.01** |
| No depression | 36.9 (215) | 11.7 (30) | 52.7 (99) | 62.8 (86) | |
| Mild-moderate depression | 56.3 (328) | 84.4 (217) | 42 (79) | 23.4 (32) | |
| Severe depression | 6.7 (39) | 3.9 (10) | 5.3 (10) | 13.9 (19) | |
| Current lithium use, yes % (n) | 25.6 (126) | 9.9 (22) | 19.4 (26) | 57.4 (78) | 103.36 (2) <.01** |
| Current antipsychotics use, yes %(n) | 53.6 (262) | 66.7 (148) | 40.3 (54) | 45.1 (60) | 28.62 (2) <.01** |

*Note.* Statistical tests were based on ANOVA or $X^2$ between the MADRS, HAM-D and CES-D sample. GAF, Global Assessment of Functioning; MADRS, Montgomery Åsberg Depression Rating Scale; HAMD, Hamilton Depression Rating Scale; CES-D, Center for Epidemiologic Studies Depression; YMRS, Young Mania Rating Scale; M = mean; SD = standard deviation; * p <0.05 ; **p <.01

(*SD* = 6.3). The three subsamples differed in terms of BD diagnosis type (BD-I vs BD-II), duration of disease, being a current smoker, lifetime psychiatric hospitalizations and GAF scores. The MADRS subsample had the most participants with a BD-I diagnosis (74.3%), the most lifetime psychiatric hospitalizations (*M* = 5.2, *SD* = 7.6) and the lowest GAF-scores (*M* = 59.3, *SD* = 10.4). The HAM-D sample had the fewest current smokers (26.1%), and the CES-D sample had the longest duration of disease (*M* = 35.3, *SD* = 13.7). The total sample had a mean YMRS score of 6.0 (*SD* = 6.0). The MADRS sample had the highest YMRS score (*M* = 7.2; *SD* = 5.2), but all samples had a YMRS score below the cut-off (≤12) on average, indicating no clinical meaningful mania symptoms at the time of testing. The HAM-D sample had the highest percentage of working participants (46.6%) when compared to the MADRS (13%) and the CES-D (24.4%) samples. The MADRS had the lowest percentage current lithium usage (25.6%), but the highest percentage antipsychotics usage (66.7%).

## Depression scores

The MADRS subsample had a mean depression score of 18.5 (*SD* = 9.3). Of these patients, 11.7% had no depression, 84.4% had mild-moderate depression and 3.9% had severe depression. The HAM-D subsample had a mean depression score of 8.6 (*SD* = 8.1). In this sample, 52.7% had no depression, 42% had mild-moderate depression and 5.3% had severe depression. The CES-D subsample had a mean depression score of 15.4 (*SD* = 9.7). 62.8% had no depression, 23.4% had mild-moderate depression and 13.9% had severe depression.

## The association between depression and functioning

Across all three subsamples, higher depression was related to significantly worse functioning for all measures, and the effect sizes and adjusted $R^2$ were larger for the continuous measures than for the categorical measure of depression severity (Table 2). Effect sizes, overall variance explained, and standardized parameter estimates (robust SE) were larger for MADRS ($^2$ = .401, $R^2$ = .525, -.74 (.11)) than either HAM-D ($^2$ = .144, $R^2$ = .369, -.51(.22)) or CES-D ($^2$ = .100, $R^2$ = .122, - .41 (.12)) in the context of generally higher depression severity and worse functioning in the MADRS subsample.

The difference between effect sizes for the continuous and categorical variables was least for HAM-D and CES-D (respectively about 6% and 2% less variance associated with the categorical depression severity predictor) and somewhat higher for MADRS (about 14% less variance associated with the categorical variable). Finally, the effect size and variance associated with the model for the harmonized depression severity score in the full sample ($^2$ = .137, $R^2$ = .291) was higher than both the categorical and continuous measure in the CES-D subsample, and lower than both the categorical and continuous measures in the HAM-D and MADRS subsample (Table 2).

**Table 2:** Subgroup comparison of effect sizes (continuous vs categorical depression classification)

| | Partial eta squared | Adjusted $R^2$ | Parameter estimated for standardized continuous and for no and mild-moderate depression (robust SE) | | Estimated marginal means of GAF (SE) | | |
|---|---|---|---|---|---|---|---|
| | | | | | No depression | Mild – moderate depression | Severe depression |
| **Total sample** | | | | | | | |
| Categorical | .137 | .291 | 7.15 (3.88) | 2.25 (4.13) | 70.10 (.87) | 59.28 (.87) | 51.69 (2.03) |
| **MADRS sample** | | | | | | | |
| Continuous | .401 | .525 | -.74 (.11) | | | | |
| Categorical | .235 | .386 | 25.71 (5.30) | 14.51 (4.96) | 75.23 (1.63) | 58.96 (.90) | 49.04 (2.59) |
| **HAM-D sample** | | | | | | | |
| Continuous | .144 | .369 | -.51 (.22) | | | | |
| Categorical | .083 | .311 | 7.37 (9.17) | 2.65 (9.24) | 68.31 (1.52) | 56.88 (1.52) | 49.33 (3.98) |
| **CES-D sample** | | | | | | | |
| Continuous | .100 | .122 | -.41 (.12) | | | | |
| Categorical | .106 | .101 | 11.21 (4.00) | 4.13 (4.56) | 67.70 (1.28) | 60.84 (2.01) | 57.85 (2.77) |

*Note.* MADRS = Montgomery Asberg Depression Scale; HAM-D = Hamilton Depression Scale; CES-D = Center for Epidemiological Studies Depression Scale; SE = Standard error; GAF = Global Assessment of Functioning.

## DISCUSSION

This study investigated the potential of harmonizing different depression scales and illustrated this by assessing the different associations between continuous and categorical measures of depression symptom severity and functioning. To our knowledge, this is the first study harmonizing different measurements of depression symptom severity in OABD and relating it to functioning. Confirming our hypothesis, we found that associations were larger for the continuous versus the harmonized categorical versions of the depression scales; however, the difference was relatively small. Higher depressive symptom severity was associated with worse functioning for all depression measures – continuous, categorical, and harmonized categorical. Therefore, harmonizing different depression scales into clinically relevant categories appears feasible without greatly reducing effect sizes.

The harmonized ordinal categorization of depression severity explained 14% of variance in functioning in the total sample, in the context of an overall model capturing only moderate variance perhaps because of greater heterogeneity between contributing studies than in the subsamples that used the same instruments. These results suggest an adequate tradeoff between the reduced granularity of measures required for harmonization and the enhanced power of a larger sample size.

When comparing the three different rating scales, the MADRS explained the most variance regarding functioning. A possible explanation can be found in the fact that the MADRS sample had relatively high depression scores. With higher depression scores, it might be the case that more aspects of daily functioning are affected. Therefore, the association between depressive symptoms and functioning might be stronger in more depressed samples. The MADRS sample also had the lowest age, therefore this sample most likely has the most working individuals. The GAF has several items that capture one's occupational functioning, whereas this instrument might therefore explain less variance in samples with less working individuals. The GAF might therefore also not be the most applicable instrument to indicate functioning in older adults. An instrument that is modified for older adults might be more appropriate, for instance the FAST-O[19]. Another explanation might be found in differences in the individual items on the depression scales. Whereas depression scales are often regarded as being interchangeable with each other, each depression scale has its own focus. Moreover, as the scales are scored by the sum of the items, each instrument is therefore biased towards symptoms covered by more items. The MADRS scale focuses primarily on criteria as described in the DSM-5. By comparison, the HAM-D includes more diverse aspects of depression, for instance, somatic and anxiety symptoms. Therefore, the HAM-D might be problematic in patients with more extensive somatic comorbidity

in whom it might be a challenge to discriminate between somatic and depressive symptoms. An earlier study[20] also showed that the HAM-D appears to be an unreliable measure of depression severity in older adults with physical illness, and that the MADRS may be a more appropriate measurement of depression severity in this population.



We found that the CES-D explained less variance in functioning when compared to the HAM-D and MADRS. It is important to note that the CES-D is a self-rated scale as opposed to the other scales, which are clinician-rated. Since the functioning scale was also clinician-rated, this might explain the difference in associated variance. Due to the highest amount of explained variance the MADRS might be preferred in clinical trials. However, the difference in explained variance between the HAM-D and the CES-D was relatively small and supports the relative utility of the CES-D. The CES-D might be particularly useful when limited resources are available to administer depression severity ratings. Whereas these different forms of assessment have pros and cons, with both self-report and clinician rated instruments were found to provide unique information that is relevant to clinical prognosis[21]. These instruments thus seem to have complementary roles in the assessment of patients with depressive symptoms.

Limitations of our analyses are typical for secondary analyses using archival data from different sources. All included studies have different inclusion and exclusion criteria, study designs, and differ in aspects of sociodemographic variables. In addition, the studies that were included were conducted in different countries, thereby including different, but validated translations of the used questionnaires. Also, our integrated sample mostly included older individuals with mild to moderate depression—this might limit the generalizability of our results to individuals with more severe depression and younger individuals. Most of the studies that contributed to our data were conducted in the United States and the Netherlands. All studies but one were conducted in the United States and the Netherlands, therefore our sample mostly consists out of WEIRD people (white, educated, industrialized, rich, and democratic[22]). This also limits the generalizability of our results. Our samples also differed on severity of disease burden, which are factors that are very likely related to functioning and whereas we were not able to include this potential source of variance in the analyses. In addition, there was also a difference between the time to which the different depression scales refer (i.e., fifteen days versus one week). This might have caused a bias in the interpretation of our results.

Our results emphasize the possibility of harmonizing different scales to create large, integrated samples. Larger samples are necessary in studying factors related to core elements of OABD and to account for the great heterogeneity in this group, while retaining statistical power. Our findings also have specific clinical implications. Since we found that the MADRS explained more variance in functioning than the CES-D and

HAM-D, it might therefore be used by clinicians preferentially when functioning is assessed, perhaps particularly in samples where the average severity of depression is high. Additionally, clinicians need to be aware that different scales are biased towards different aspects of depression and are therefore not necessarily interchangeable. Accordingly, future research could investigate how the differential factor structure of each depression scale influences mood symptom ratings and their associations with daily functioning in OABD.

In conclusion, the current study illustrates the potential utility of harmonizing different depression rating scales, without losing statistical power. By successfully harmonizing these different depression measures, we found that more depressive symptoms were associated with worse functioning in OABD. Since the OABD population is growing at a population level, it is essential to gain more knowledge about this vulnerable group. Future research might therefore explore these harmonization methods in relation to different cognitive measures to study the relationship between cognition and functioning in this group, and to investigate potential subgroups accounting for heterogeneity.

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# CHAPTER 3

# Reliability and validity of the Functioning Assessment Short Test for Older adults with bipolar disorder (FAST-O)

Melis Orhan, Nicole Korten, Ralph Kupka, Patricia van Oppen, Max Stek, Eduard Vieta, Sigfried Schouws, Wouter van Ballegooijen & Annemiek Dols

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## ABSTRACT

**Background:** Many frequently used instruments fail to assess psychosocial functioning in patients with bipolar disorder. The Functioning Assessment Short Test (FAST) was developed in order to tackle this problem and to assess the main functioning problems experienced by patients with bipolar disorder. However, the original FAST is not fully applicable in older adults due to the domain of occupational functioning. The aim of our study was to validate an adapted version for older adults (FAST-O) in a group of older adults with bipolar disorder (OABD).

**Methods:** 88 patients aged 50 years and over diagnosed with bipolar disorder were included. We adapted the items in the area of "work-related functioning" of the FAST into items assessing "socetal functioning". Several measurements were conducted in order to analyse the psychometric qualities of the FAST-O (confirmatory factor analysis for internal structure, Cronbach's alpha for internal consistency, Spearman's rho for concurrent validity, Mann-Whitney U test for discriminant validity).

**Results:** Mean age in the study sample was 65.3 (SD = 7.5) and 57.3% was female. The internal structure was most similar to the internal structure of the original FAST. The internal consistency was excellent (Cronbach's alpha = .93). The concurrent validity when correlated with the Social and Occupational Functioning Assessment Scale was low, but significant. The FAST-O was also able to distinguish between euthymic and symptomatic OABD patients.

**Discussion:** The FAST-O has strong psychometric qualities. Based on our results, we can conclude that the FAST-O is a short, efficient solution in order to replace global rating scales or extensive test batteries in order to assess daily functioning of older psychiatric patients in a valid and reliable manner.

# INTRODUCTION

Bipolar disorder (BD) is a severe, episodic, lifelong mood disorder that is defined by episodes of mania or hypomania alternating or occurring concomitantly with depressive episodes, and euthymic phases[1]. Although the prevalence of BD seems to decline with age, still 8-10% of psychiatric inpatients over age 55-60 are diagnosed with BD[2].Contrary to the traditional view that individuals with BD are asymptomatic between episodes and return to normal functioning, recent studies have revealed a much less optimistic picture[3]. Many patients with BD in clinical remission experience residual mood symptoms, social dysfunction, cognitive impairment and stigma[4]. As a result, 30 – 60% of adult patients with BD suffer from poor psychosocial functioning[5]. Functioning is a complex construct that involves many interactions and activities in personal, occupational, and recreational contexts[6,7]. Therefore, formulating a clear definition is often a challenge. The ICF identifies three levels of human functioning: functioning at the level of body or body part, the whole person, and the whole person in a social context. Disability therefore involves dysfunction at one or more of these same levels: impairments, activity limitations and participation restrictions[8]. In older age BD (OABD), functioning may become further limited as a result of various factors, such as a decreasing social network size and reduced mobility[9]. Social functioning is also related to cognitive functioning[10], which is worse in OABD patients compared with healthy controls[11].

Due to a lack of easy-to-use instruments, patients need to undergo an extensive battery of tests to fully assess all the relevant factors regarding daily functioning, which is time-consuming for both patient and therapist. Besides these extensive batteries, the currently most frequently used measures to assess daily functioning are global rating scales. However, these fail to distinguishing clinical and functional recovery[12] and do not include all areas of daily functioning. To tackle this problem, experts of the Bipolar Disorder Program (Barcelona, Spain) identified six main areas of problems experienced by patients with BD, including autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time[2]. Subsequently, these findings were used to design the Functioning Assessment Short Test (FAST); a quick and easily administrable instrument for the clinical evaluation of daily impairments presented by patients suffering from BD[13]. However, in older adults the FAST may not be fully applicable given the questions in the domain of occupational functioning. In the original FAST manual[13], some suggestions were proposed to alter the items on the occupational scale for patients whose occupational functioning cannot be rated. In line with these suggestions, we adapted the FAST for the OABD population into the FAST-O, the Functioning Assessment Short Test for Older adults (FAST-O). Hereby the domain of occupational functioning was altered slightly and items on the original

FAST were translated to Dutch. The FAST has been validated in several languages for adult patients with BD and these studies all show similar positive results regarding its reliability and validity[14,15,16]. However, to date the FAST has not been validated in an OABD sample. The aim of this study was therefore to validate the Dutch version of the FAST in the assessment of functional impairments in a group of OABD.

# METHODS

## Study sample

The sample of this cross-sectional study included OABD patients from the Amsterdam mental health catchment area. Data were used from the Dutch Older Bipolars (DOBi) dynamic cohort study[17]. A computerized search into the electronic record-keeping system of the Mental Health Organization identified all patients aged ≥ 50 in contact with health services, who had any registered diagnosis that could indicate BD. Medical records were screened by a psychiatrist for exclusion criteria: not being able to give written informed consent, not being able to communicate in Dutch, mental retardation (IQ < 70), poor cognitive performance (MMSE <18), or a highly unstable psychiatric condition. Inclusion was possible when participants were clinically diagnosed by their treating therapist with bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified. We included 88 patients in total. The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, Netherlands.

## Demographic and clinical characteristics

Sociodemographic data were obtained by interview. Diagnosis, type of bipolar disorder, and age at first depressive or (hypo)manic episode were established by the Mini-International Neuropsychiatric Interview Plus (MINI-plus[18]). The number of psychiatric admissions was obtained by clinical interview. Current mania symptoms were assessed through the Young Mania Rating Scale (YMRS[19]). The YMRS is scored on a scale from 0 to 60 with scores ≥ 12 indicating clinically relevant (hypo) mania. Current symptoms of depression were measured by the Centre for Epidemiologic Studies Depression Scale (CES-D[20]), a 20-item self-report scale measuring severity of depressive symptoms during the previous week, with scores ranging from 0 to 60. Scores ≥ 16 indicate clinically relevant depression. To assess psychosocial functioning, the Social and Occupational Functioning Assessment Scale (SOFAS[21]) was conducted. The SOFAS scores the level of global social functioning in the previous week, as estimated by patients' treating psychiatrist. The achieved score is a global rating of current social functioning ranging from 1 to 100, with lower scores indicating lower social functioning and scores ≥ 90 suggesting no social impairments. All tests were administered by trained research assistants.

## Functioning Assessment Short Test (FAST)

The FAST was originally developed to assess the main problems in functioning experienced by psychiatric patients, particularly BD patients[13]. The FAST was translated in Italian[22], Portuguese[23], Turkish[24], Finnish[15] and Chinese[16]. It comprises 24 items divided into six aspects of daily functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. The FAST is an interviewer-administered instrument, and is designed to be conducted by a trained clinician. The studied time frame refers to the last 15 days before the assessment. In order to make the instrument more applicable for the older age population, we have replaced the domain of occupational functioning by the domain of societal functioning and therefore altered three items. We altered item 5 from "holding down a paid job" to "holding down meaningful daytime activities", item 7 from "working in the field in which you were educated" to "working (paid of voluntary), including taking care of grandchildren or taking care of a family member" and item 8 from "occupational earnings" to "earnings (from work or payment/retirement fund)". All items are rated using a 4-point scale, 0 = no difficulty, 1 = mild difficulty, 2 = moderate difficulty and 3 = severe difficulty. The overall score is the sum of all items, whereby higher scores indicate more serious impairment. The number of items in the FAST-O was equal to the number of items in the original FAST. See Table 1 for the FAST-O. The FAST-O is easy to administer and can be administered by any trained health care professional. The time it takes to administer the FAST-O is around 15 minutes.



## Statistical analyses

Data were analysed using the Statistical Package of the Social Sciences (version 24.0, SPSS Inc., Chicago, IL, USA) and R[25] (version 3.5.3). Internal consistency was analyzed using Cronbach's alpha for the total scale and for each subscale. Concurrent validity was assessed by calculating Spearman's rho between total FAST scores and SOFAS scores. The SOFAS was chosen as an instrument to investigate concurrent validity, since it is often used as a measurement for global social functioning in mental disorders. Validity as a discriminant measure to detect differences in FAST scores between euthymic and symptomatic patients was also assessed. This was done by dividing patients by their symptom severity scores (YMRS & CES-D scores) into a euthymic and a symptomatic group. Symptomatic patients were identified by having scores above cut-off on the YMRS and CES-D, respectively equal and above 12 and 16. A Mann-Whitney U test was used to evaluate whether the FAST total scores were sensitive to the severity of symptoms. The internal structure of the FAST was studied by conducting a confirmatory factor analysis with a number of fixed factors based on the internal structure of the original FAST[12]. Several confirmatory factor analysis (CFA) models were estimated, based on previously estimated models in other studies studying the internal structure of the FAST. All estimations were conducted in *R*[24]. We used the comparative fit index (CFI), Tucker-Lewis index (TLI), Akaike (AIC), Bayesian (BIC) and Root Mean Square Error of Approximation (RMSEA) as fit indices.

**Table 1:** The Functioning Assessment Short Test for Older adults (FAST-O)

| To what extent is the patient experiencing difficulties in the following aspects? | | | | | |
|---|---|---|---|---|---|
| | | **No difficulty** | **Mild difficulty** | **Moderate difficulty** | **Severe difficulty** |
| | **Autonomy** | | | | |
| 1 | Taking responsibility for a household | 0 | 1 | 2 | 3 |
| 2 | Living on your own | 0 | 1 | 2 | 3 |
| 3 | Doing the shopping | 0 | 1 | 2 | 3 |
| 4 | Taking care of yourself (physical aspects, hygiene) | 0 | 1 | 2 | 3 |
| | **Societal functioning** | | | | |
| 5 | Maintaining meaningful daily activities | 0 | 1 | 2 | 3 |
| 6 | Accomplishing tasks as quickly as necessary | 0 | 1 | 2 | 3 |
| 7 | Working (in a paid or voluntary job), including taking care of grandchildren and informal care | 0 | 1 | 2 | 3 |
| 8 | Income (occupational earnings or income from retirement) | 0 | 1 | 2 | 3 |
| 9 | Managing the expected work load or other tasks | 0 | 1 | 2 | 3 |
| | **Cognitive functioning** | | | | |
| 10 | Ability to concentrate on a book, film | 0 | 1 | 2 | 3 |
| 11 | Ability to make mental calculations | 0 | 1 | 2 | 3 |
| 12 | Ability to solve a problem adequately | 0 | 1 | 2 | 3 |
| 13 | Ability to remember newly-learned names | 0 | 1 | 2 | 3 |
| 14 | Ability to learn new information | 0 | 1 | 2 | 3 |
| | **Financial issues** | 0 | 1 | 2 | 3 |
| 15 | Managing your own money | 0 | 1 | 2 | 3 |
| 16 | Spending money in a balanced way | 0 | 1 | 2 | 3 |
| | Interpersonal relationships | | | | |
| 17 | Maintaining a friendship or friendships | 0 | 1 | 2 | 3 |
| 18 | Participating in social activities | 0 | 1 | 2 | 3 |
| 19 | Having good relationships with people close to you | 0 | 1 | 2 | 3 |
| 20 | Living together with your family | 0 | 1 | 2 | 3 |
| 21 | Having satisfactory sexual relationships | 0 | 1 | 2 | 3 |
| 22 | Being able to defend your interests | 0 | 1 | 2 | 3 |
| | **Leisure time** | | | | |
| 23 | Doing exercise or participating in sport | 0 | 1 | 2 | 3 |
| 24 | Having hobbies or personal interests | 0 | 1 | 2 | 3 |

# RESULTS

## Study sample

Summary of the demographic and clinical characteristics is shown in Table 2. Participants had a mean age of 65.3 (*SD* = 7.5), 57.3% was female and 42.7% was male. Of all participants, 76% had the Dutch nationality. Level of education was divided into three levels: low, medium and high. For 49.4%, the level of education was high. Of all participants, 30.5% was still in active paid employment. The 69.5% that was not in active paid employment was divided into 32.9% that was retired and 36.6% that was unemployed at the time of testing. The 69.5% that was not in active paid employment at the time of testing, was divided into 32.9% that was retired and 36.6% that was unemployed at the time of testing. Participants had an average of 14.8 (*SD* = 42.6) self-reported manic and 19.9 depressive episodes (*SD* = 39.7). The mean SOFAS score was 64.3 (*SD* = 14.8), indicating that our group had mild impairments in social functioning. Mean YMRS score was 3.1 (*SD* = 3.8) and mean CES-D score was 13.4 (*SD* = 11.8), indicating that on average, no significant mood symptoms were present at the time of investigation. 36.1 percent of all participants had a score of 16 or higher on the CES-D, indicating a clinically relevant depression. 4.5 percent of all participants had a score of 12 or higher on the YMRS, indicating a clinically significant (hypo)mania. Participants had an average score of 15.9 (*SD* = 13.8) on the FAST-O, with scores ranging from 0 to 68. Average scores on each subscale are found in Table 2.

## Psychometrics

*Internal structure*

In order to compare the internal structure of the FAST-O, we conducted multiple confirmatory factor analyses according to the factor analyses conducted in earlier studies on different versions of the FAST[12,22,25]. The proposed model that showed the best fit when compared to our FAST-O, was the model that was also found in the original FAST article[12]. Results are shown in Table 3. This study determined a five-factor structure, whereby it was observed that social functioning and interpersonal relationships were loading on the same factor. Concerning our internal structure, the CFI and TLI were respectively 0.88 and 0.86, indicating a medium fit. The Root Mean Square Error of Approximation (RMSEA) was 0.083 with a 90% CI 0.075 until 0.105.

**Table 2:** Demographic and clinical variables of the study sample

| Variable | |
|---|---|
| Age, M(SD), range | 65.33 (7.45), 51.3 – 86.8 |
| Gender, female, % (n) | 57.3 (47) |
| Nationality, Dutch, % (n) | 86.4 (76) |
| Level of education, high % (n) | 50.4 (41) |
| In active paid employment, yes, % (n) | 30.5 (25) |
| Number of depressive episodes, M (SD), range | 19.89 (42.57), 1 – 300 |
| Number of manic episodes, M (SD), range | 14.83 (39.7), 1 – 300 |
| CES-D, M (SD), range | 13.35 (11.84), 0 – 51 |
| YMRS, M (SD), range | 3.09 (3.78), 0 – 18 |
| SOFAS, M (SD), range | 64.31 (14,84), 40 – 100 |
| FAST-O | |
| Total score, M (SD), range | 15.93 (13.84), 0 – 68 |
| Autonomy score, M (SD), range | 1.88 (2.80), 0 – 13 |
| Societal functioning score, M (SD), range | 3.3 (3.9), 0 – 19 |
| Cognitive functioning score, M (SD), range | 5.29 (4.18), 0 – 20 |
| Interpersonal relationships score, M (SD), range | 4.58 (4.32), 0 – 18 |
| Leisure time score, M (SD), range | 1.39 (1.73), 0 – 7 |

*Note*. *M* = mean, *SD* = standard deviation, CES-D = Centre for Epidemiologic Studies Depression Scale, YMRS = Young Mania Rating Scale, SOFAS = Social and Occupational Functioning Assessment Scale, FAST-O = Functioning Assessment Short Test for Older adults

*Reliability*

Internal consistency was measured by Cronbach's alpha. For the total scale, Cronbach's alpha was .93 indicating an excellent internal consistency. No individual items can be deleted to attain a higher Cronbach's alpha. When looking at the different domains, a high internal consistency was found for autonomy (Cronbach's alpha = .84), with all inter-item correlations > .50. A high internal consistency was also found for the domain of social functioning (Cronbach's alpha = 0.85), with all inter-item correlations > .36. This was also found for cognitive functioning (Cronbach's alpha = .83), with a lowest inter-item correlation of .39. For financial functioning was an excellent internal consistency found (Cronbach's alpha = .92), with an inter-item correlation of .85. The domain of interpersonal functioning showed a high internal consistency of .82, with a lowest inter-item correlation of .18. The last domain of leisure time had a medium internal consistency with a Cronbach's alpha of .62, and an inter-item correlation of .46.

*Concurrent validity*

Concurrent validity based on functional impairment according to the SOFAS scale showed a low significant correlation between SOFAS scores and FAST-O scores (Spearman's rho = -.33; $p < .01$).

**Table 3:** Factor loadings of the items of the FAST-O

| FAST | Autonomy factor | Psychosocial factor | Cognitive factor | Financial factor | Interpersonal / Leisure factor |
|---|---|---|---|---|---|
| Item 1 | 0.766 | | | | |
| Item 2 | 0.749 | | | | |
| Item 3 | 0.877 | | | | |
| Item 4 | 0.841 | | | | |
| Item 5 | | 0.775 | | | |
| Item 6 | | 0.845 | | | |
| Item 7 | | 0.750 | | | |
| Item 8 | | 0.652 | | | |
| Item 9 | | 0.809 | | | |
| Item 10 | | | 0.718 | | |
| Item 11 | | | 0.591 | | |
| Item 12 | | | 0.836 | | |
| Item 13 | | | 0.699 | | |
| Item 14 | | | 0.823 | | |
| Item 15 | | | | 0.934 | |
| Item 16 | | | | 0.901 | |
| Item 17 | | | | | 0.778 |
| Item 18 | | | | | 0.767 |
| Item 19 | | | | | 0.819 |
| Item 20 | | | | | 0.675 |
| Item 21 | | | | | 0.453 |
| Item 22 | | | | | 0.664 |
| Item 23 | | | | | 0.605 |
| Item 24 | | | | | 0.700 |

*Discriminant validity*

A Mann-Whitney U test was used as a discriminant measure to explore the difference in scores between euthymic patients and symptomatic patients. The Mann-Whitney U test was significant ($p < .01$), indicating that scores on the FAST-O are different between symptomatic and euthymic patients. By calculating the ROC curve, we further explored the discriminant capacity between symptomatic and euthymic patients. The area under the curve was 0.77 (95% CI .65 – 90; $p < .01$), indicating a good capacity. Also was observed that a score above 9.5 the best balance obtains between sensitivity (87%) and specificity (74%). In the original FAST[13] similar scores were found, where the best balance was obtained between sensitivity (72%) and specificity (87%) with a score above 11.

## DISCUSSION

The aim of this study was to study the psychometric qualities of the FAST-O in an OABD population. We found that the FAST-O proved to be a reliable and valid measure, when adapting the items to an OABD patient sample. The instrument showed an excellent internal consistency and was successful in discriminating between symptomatic and euthymic patients. The concurrent validity was significant. The internal structure of the FAST-O showed a satisfactory fit when compared to the original FAST. Our results indicate that the FAST-O can be used as a quick and easy way to assess daily functioning in OABD patients.

Given the lack of short, practical instruments to assess daily functioning in OABD, we altered the original FAST with regard to the area of work for the use in an older patient population. The original FAST[13] was already well-studied in several languages[22,23,24,15,16] and studies investigating psychometric qualities when used in the adult population showed positive results. In previous studies, the correlation between the FAST and the SOFAS scale was studied to assess the concurrent validity indicating a good concurrent validity. Our correlation coefficient was low in comparison with correlation coefficients found in other studies. This difference may be due to the fact that the SOFAS scale is a rating scale based on functioning in social, but also in occupational domains thereby more suited for working age adults. In our sample, only 30.5% was still in active paid employment and the SOFAS is therefore not completely suitable for these participants. The retirement age in the Netherlands is currently 67 but relatively good social networks (still) exist for those leaving a paid job before reaching this official retirement age. Also, the SOFAS assesses impairments in social and occupational functioning that are a result of the mental disorder. In the FAST-O, the term occupational functioning is replaced by societal functioning thereby shifting the focus of the rated area. Thereby, the FAST-O does not make an distinction between problems in daily functioning as a direct result of the mental health problems, but sketches a more global view of daily functioning. The FAST-O and the SOFAS therefore measure different concepts. However, we decided to draw a comparison with the SOFAS, since it is currently the most frequently used rating scale in mental health care to indicate daily functioning.

When looking into the internal structure of the FAST-O, we found that the adjusted items have high factor loadings on the same five factor as the corresponding items in the original FAST[13]. This indicates that the items that we altered for use in the older patient population resemble the same internal structure as the original items. All in all, the FAST-O has proven to be a well-suited alternative to more extensive assessment batteries in order to assess daily functioning.

In our study, we included patients of 50 years and over and the majority of our group was not in active paid employment. However, the items are also applicable to populations where a part of the population is still in active paid employment. But since the items are more applicable for patients who are not in active paid employment, we recommend using this instrument for these patients. In populations where the majority is still in active employment, we recommend using the original FAST[13].



Our study has several limitations. First, we did not take into account different age and ethnic groups nor responsiveness over time in order to draw a conclusion about the ecological validity of the FAST-O. We also did not take into account a measure of test-retest reliability. Finally, we used a relatively small sample with light to moderate symptoms. Therefore, our results should be interpreted with caution. Still, our study also has several strong points. Until now, no other short instrument has been developed for the assessment of daily functioning in the older patient population, and our results are promising. The authors of the original FAST article published another study in which they determined specific cut-off points for the FAST[27]. In line with the work of these authors, future research should therefore focus on investigating specific cut-off points for the FAST-O in order to draw more standardized conclusions about the current level of daily functioning.

## CONCLUSIONS

In conclusion, the FAST-O has good psychometric qualities and therefore shows good validity and reliability. The FAST has already been extensively studied in the adult population, with good results in several languages. Adapted as FAST-O, it can be used in older patient populations to assess daily functioning in a practical and time-efficient manner.

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# CHAPTER 4

# Cognitive functioning in late life affective disorders: Comparing older adults with bipolar disorder, late life depression and healthy controls

Melis Orhan, Sigfried Schouws, Patricia van Oppen, Max Stek, Paul Naarding, Didi Rhebergen, Annemieke Dols & Nicole Korten

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## ABSTRACT

**Background:** Both older age bipolar disorder (OABD) and late life depression (LLD) have been associated with cognitive dysfunction. It is unclear how cognitive functioning differs between these disorders and what the influence of current depressive symptoms is.

**Methods:** We compared OABD (n = 148), LLD (n = 378) and healthy controls (HC) (n = 132) on cognitive functioning. Cognitive functioning was measured by an extensive neuropsychological assessment, and divided into four domains: episodic memory, processing speed, interference inhibition and working memory. Separate linear regression analyses were conducted with OABD as reference category, controlling for age, gender, level of education and severity of depressive symptoms.

**Results:** Our findings show that OABD and LLD patients exhibit more cognitive dysfunction than HC, with OABD showing worst cognitive functioning on all cognitive domains, except for interference inhibition. These differences remained significant, even after controlling for the effect of depressive symptoms at the time of testing.

**Discussion:** Our findings suggest that cognitive dysfunction in OABD is more severe in magnitude albeit in the same domains as in LLD. This difference cannot be fully explained by the severity of depressive symptoms. Future research should focus on other disease characteristics and how these characteristics are associated with the complex concept of cognitive functioning in both OABD and LLD.

# INTRODUCTION

Affective disorders in older adults are highly disabling, resulting in a higher prevalence of somatic comorbidities, cognitive deficits and overall mortality[1]. Affective disorders, including bipolar disorder (BD) and major depressive disorder (MDD), have an episode of depression with a high risk on recurrence[2,3,4] in common but are divided in separate chapters in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5[5]). The strongest support for this division seems to come from differences in symptomatology (manic episodes in BD) and response to pharmacological treatment[5,6]. Combined with differences in brain structure and neural activity[7,8], this different symptomatology and pathophysiology is suggested to have consequences for cognitive functioning[9].



Both OABD and LLD have been associated with cognitive dysfunction[10,11,12], with negative consequences for daily functioning[13,14,15]. A recent meta-analysis showed that OABD show important deficits in almost all cognitive domains, especially in the memory domain[16]. Also, cognitive impairments in LLD are well-established and consistently found in three primary cognitive domains: processing speed, attention and executive functioning[17,18,19].

The debate remains whether these cognitive impairments are a result of the depressive symptoms or whether they are a result of other disease mechanisms. In OABD, it is proposed that cognitive impairments are a result of toxic mood episodes, e.g. neuroprogression[20,21] which is associated with increased dementia prevalence[22]. Cognitive impairments in LLD were previously considered as an integrational part of the mood symptomatology, whereas more recent studies show that cognitive impairment is not only a manifestation of depression but also remain present during remission[23].

To date, most studies investigate cognitive functioning in OABD and LLD separately, hampering direct comparisons. A meta-analysis[6] in an adult population, stated that BD subjects had more severe neuropsychological impairment than MDD subjects in terms of affected domains and magnitude, but that better-matched affective disorder samples are necessary to draw more robust conclusions. In the older patient population, only one study has studied both groups simultaneously. In this study[24], 43 OABD patients, 122 LLD patients and 92 healthy controls (HC) were compared. Results showed that OABD patients and LLD patients were more impaired in all cognitive domains in comparison with HC. In addition, OABD patients were more impaired than LLD patients on all cognitive domains.

Up until now, there is a lack of clinically available treatments for cognitive impairment in BD and UD[25,26]. Investigating cognitive functioning in OABD and LLD might contribute to better understanding of cognitive functions in these disorders and support development of treatment strategies and prevention of additional functional impairment. In order to replicate findings of an earlier study[24], we compared cognitive functioning between OABD, LLD and HC in a larger sample. Additionally, the former study[24] did not include current depressive symptoms in their analyses. The aim of our study was therefore two-folded; our first aim was to investigate cognitive functioning in these three groups and compare the affected domains and severity of dysfunction. Our second aim was to investigate whether expected differences in cognitive functioning can be explained by current depressive symptoms, by including these in our analyses. Similar to the findings of the former study[24], we expected that OABD patients and LLD patients show worse cognitive functioning in comparison with HC, and OABD patients show most impaired cognitive functioning in all domains. In addition, we expected that depressive symptoms will partly explain the difference in cognitive functioning between the three groups.

# METHODS

## Participants

Three groups of participants were included, derived from two different cohort studies. OABD patients were derived from the Dutch Older Bipolars (DOBi) cohort study, and were recruited in 2012 and 2017/2018. A more extensive description of the DOBi study is elsewhere presented[27]. Included participants were 50 years and over. A current diagnosis of BD I, BD II or BD not otherwise specified was assessed with the MINI International Neuropsychiatric Interview (MINI) Plus[28]. Exclusion criteria for OABD were a dementia diagnosis, intellectual inability (IQ < 70), a language barrier, very poor cognitive functioning (Mini Mental State Examination-score; MMSE < 18) or an insufficiently stable psychiatric condition to undergo the assessments. Additionally, LLD patients were derived from the Netherlands Study of Depression in Older Persons (NESDO[29]) and were included when they fulfilled the DSM-IV criteria for major depression (95.0%), dysthymia (26.5%), or minor depression (5.0%)[5] and the diagnosis was present in the six months before inclusion. These diagnoses were assessed with the Composite International Diagnostic Interview (CIDI[30]; World Health Organization version 2.1; lifetime version). The healthy control group was also derived from the NESDO study, and consisted of a group of persons without a lifetime diagnosis of unipolar or bipolar depression. Data collection started in 2007 and was finished in 2010. Exclusion criteria for LLD and HC were a primary diagnosis of dementia, psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder, MMSE < 18, and

insufficient command of the Dutch language. A more extensive description of the NESDO study is published elsewhere[29]. NESDO participants were recruited between 2007 and 2010.

All included patients and HC were asked to provide written consent for participation in DOBi or NESDO. Participants of 60 years and over were included in the current study (n= 663), among which were 148 OABD patients, 378 LLD patients and 132 HC. The study was approved by the Medical Ethics Committee of the Amsterdam UMC, location Vrije Universiteit, the Netherlands.

## Measurements



### *Demographic and clinical variables*

Demographic data (e.g. age, gender, educational level, partner status) were obtained through patient's medical records or interviews. Low education was defined as elementary school, medium education was defined as lower vocational education, general intermediate education, general secondary education, and high education was defined as higher vocational education, college education, and university education. The presence of BD in the OABD group was confirmed by the Mini International Neuropsychiatric Interview Plus (MINI[28]). Diagnoses in the LLD group were assessed with the Composite International Diagnostic Interview (CIDI[30]) according to DSM-IV-R criteria. For the OABD group, current mania symptoms were measured by the Young Mania Rating Scale (YMRS[31]). The YMRS is scored on a scale from 0 to 60, with scores ≥ 12 indicating clinically relevant (hypo)mania. Current symptoms of depression were measured by the Center for Epidemiologic Studies Depression Scale (CES-D[32]) in all three groups. The CES-D is a self-report scale, consisting of 20 items. It measures depressive symptoms during the previous week, with scores ranging from 0 to 60. Scores ≥ 16 indicate clinically relevant depression. Age of onset was defined as the age when participants experienced their first mood episode (manic or depressive). The medication that participants used was noted, and divided into the following categories: benzodiazepines, lithium, TCA or SSRI. The number of chronic diseases was assessed by self-report questions about the presence of somatic diseases (cardiac diseases, cerebrovascular accident, hypertension, peripheral arthosclerosis, diabetis mellitus, chronic non-specific lung disease, liver diseases, thyroid diseases, epilepsy, intestinal diseases, arthritis/arthrosis, and cancer).

### *Cognitive functioning.*

Global cognitive functioning of all patients was measured by the Mini-Mental State Examination[33]. Cognitive functioning was further divided into different domains: episodic memory, processing speed, interference score and working memory. These domains were cross-sectionally measured by a neuropsychological assessment at the

time of inclusion. Episodic memory was measured with the 10 Words Test (sum of the five learning conditions, delayed recall and a composite score[34]). Processing speed was measured with a modified version of the Stroop Color Word Test (card I, card II and a composite z-score[35]). The interference inhibition score was measured by using the difference in scores of card II and card III. Working memory was measured by the Digits test, a subtest of the Wechsler Adult Intelligence Scale (WAIS-III[36]). The forward condition, backward condition and a composite score were used. Raw scores from the separate cognitive tasks were calculated and the mean z-scores of the cognitive tasks representing one cognitive domain were used.

### Statistical analyses

Data was analyzed with the Statistical Package of the Social Sciences (version 25.0, SPSS Inc., Chicago, IL, USA). Descriptive analyses were used for the demographic and clinical characteristics of our three groups. ANOVA analyses were used to compare continuous, normally-distributed variables between the three groups. When variables were not normally distributed, Kruskal-Wallis tests were conducted. Chi-square tests were conducted to compare categorical variables between the three groups. Cognitive functioning scores were included in the analyses both as raw scores per cognitive task and as composite z-score per domain. In order to compare cognitive functioning between OABD, LLD and HC, separate linear regression analyses were conducted with OABD as reference category. The raw scores on the Stroop task were transformed (1/(Stroop card I), 1/(Stroop card II), LN(Stroop interference inhibition score)) to obtain a near-normal distribution. The other cognitive measures showed a normal distribution. Age, gender and level of education were included as covariates in model 1. Additionally, the severity of depressive symptoms was included as covariate in model 2.

## RESULTS

### Demographic and clinical characteristics

The demographic and clinical characteristics for each group are summarized in Table 1. Firstly, all groups were compared with respect to demographic and clinical characteristics. OABD patients were significantly younger than LLD ($p$ <.01) and HC ($p$ = .05). OABD had a higher prevalence of males than HC ($p$ <.01) and LLD ($p$ <.01). OABD had an earlier age of onset than LLD ($M$ = 33.2, $SD$ = 14.7 vs. $M$ = 48.4, $SD$ = 20.6, $p$ < .01) and a longer disease duration ($M$ = 35.2, $SD$ = 14.1 vs. $M$ = 21.8, $SD$ = 19.9). LLD had higher depression severity than OABD ($M$ = 22.9, $SD$ = 10 vs. $M$ = 13.7, $SD$ = 6.7, $p$ < 0.01) and HC ($M$ = 6.2, $SD$ = 5.6, $p$ <.01). MMSE scores, indicating global cognitive functioning, were significantly different between the three groups, with LLD showing the lowest scores compared to HC ($M$ = 27.7, $SD$ = 2.0). OABD and HC ($p$ = .12) and OABD and LLD

also did not show a significant difference ($p$ = .15). LLD used mostly benzodiazepines (47.1%) when compared to OABD (33.8%) and HC (6.1%). OABD mostly used lithium (58.8%), when compared to LLD (3.7%) and HC (0%). LLD also used more SSRI's and TCA's (27.8% and 21.7%) than OABD (14.9% and 8.8%) and HC (0.8% and 1.5%). OABD had slightly more somatic diseases ($M$ = 2.2, $SD$ = 1.7), when compared to LLD ($M$ = 2.1, $SD$ = 1.5). HC had the least somatic diseases ($M$ = 1.5, $SD$ = 1.1). OABD had most somatic illnesses ($M$ = 2.2, $SD$ = 1.7) when compared to LLD ($M$ = 2.1, $SD$ = 1.5) and HC ($M$ = 1.5, $SD$ = 1.1). However, the difference in somatic diseases between OABD and LLD was not significant ($p$ = .61).

## Cognitive functioning



A comparison between the three groups on all cognitive domains is presented in Figure 1. Results from linear regression analyses comparing the three groups on cognitive functioning are summarized in Table 2.

### *Episodic memory*

For the composite z-score of episodic memory OABD showed more impairments than HC in both model 1 and 2 (β = .35, $p$ < .01 and β = .34, $p$ < .01), and also more impairments than LDD in both model 1 and 2 (β = .35, $p$ <.01 and β = .37, $p$ <.01).

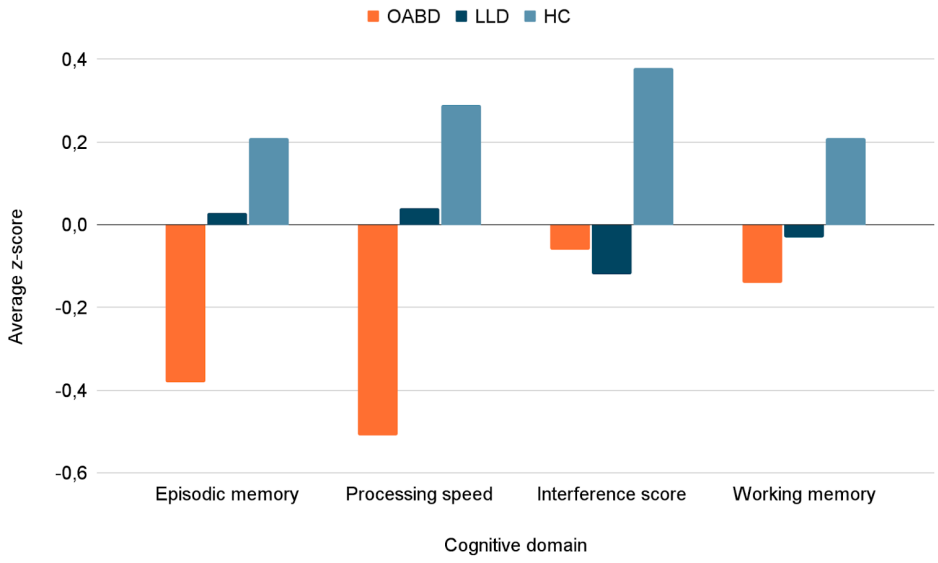


**Figure 1:** Average z-scores sorted in each cognitive domain, sorted by group

**Table 1:** Descriptive statistics of the three groups (LLD, OABD and HC)

| | **LLD (*n* = 378)** | **OABD (*n* = 148)** | **HC (*n* = 132)** | **Statistics** |
|---|---|---|---|---|
| Age, M (SD) | 70.7 (7.4), 60 – 96 | 68.4 (7.1), 60 – 96 | 70.1 (7.2), 60 – 93 | 12.4 (2) <.01** |
| Gender, female % (n), range | 66.1 (250) | 52 (77) | 61.4 (81) | 7.64 (2) .02* |
| Education, % (n) | | | | 133.5 (8) <.01** |
| Low | 43.1 (163) | 30.1 (37) | 18.9 (25) | |
| Medium | 36.0 (136) | 22.8 (28) | 41.7 (55) | |
| High | 20.9 (79) | 47.2 (58) | 39.4 (52) | |
| Age of onset, M (SD), range | 48.4 (20.6), 2 – 86 | 33.2 (14.7), 4 – 41 | - | - |
| Duration of disease, M (SD), range | 21.8 (19.9), 0 – 84 | 35.2 (14.1), 0.8 – 79.3 | - | 56.08 (1) <.01** |
| YMRS, M (SD), range | - | 5.8 (7.2), 0 – 33 | - | - |
| CES-D, M (SD), range | 22.9 (10.0), 2 – 53 | 13.7 (6.7), 4 – 41 | 6.2 (5.6), 0 – 41 | 187.4 (2) <.01** |
| MMSE, M (SD), range | 27.7 (2.0), 17 – 30 | 28 (1.9), 21 – 30 | 28.3 (1.6), 21 – 30 | 11.0 (2) <.01** |
| Digit span, M (SD), range | 9.6 (1.8), 4 – 13 | 9.3 (2.0), 5 – 14 | 10.1 (1.8), 6 – 13 | 6.1 (2) <.01** |
| Ten words test, M (SD), range | 31.4 (7.1), 11 – 46 | 29.7 (8.6), 11 – 48 | 34.3 (6.5), 14 – 48 | 13.0 (2) <.01** |
| Stroop card I, M (SD), range | 20.7 (5.8), 9 – 55 | 25.7 (17.8), 13 – 176 | 19.1 (4.3), 11 – 45 | 30.3 (2) <.01** |
| Stroop card II, M (SD), range | 26.8 (7.1), 16 – 72 | 31.9 (17.5), 17 – 164 | 23.8 (4.8), 17 – 45 | 41.0 (2) <.01** |
| Stroop card III, M (SD), range | 57.9 (25.5), 23 – 180 | 61.7 (42.6), 26 – 406 | 44.1 (13.7), 25 – 131 | 43.0 (2) <.01** |
| Stroop interference, M (SD), range | 1.4 (.8), .2 – 5.6 | 1.2 (.6), .2 – 3 | 1.1 (.4), .3 – 2.7 | 8.1 (2) <.01** |
| Benzodiazepine use, yes % (n) | 47.1 (178) | 40.5 (60) | 6.1 (8) | 72.0 (2) <.01** |
| Lithium use, yes % (n) | 3.7 (14) | 52.0 (77) | 0 (0) | 278.3 (2) <.01** |
| TCA use, yes % (n) | 21.7 (82) | 17.6 (26) | 1.5 (2) | 37.1 (2) <.01** |
| SSRI use, yes % (n) | 27.8 (105) | 14.9 (22) | 0.8 (1) | 48.2 (2) <.01** |
| Number of somatic diseases, M (SD), range | 2.1 (1.5), 0 – 8 | 2.2 (1.7), 0 – 8 | 1.5 (1.1), 0 – 4 | 10.7 (2) <.01** |

*Note.* YMRS, Young Mania Rating Scale; CES-D, Center for Epidemiologics Studies Depression Scale; SOFAS: Social and Occupational Functioning Assessment Scale; MMSE: Mini Mental State Examination; n=the number of participants; M=mean; SD=standard deviation. Statistical tests were based on $\chi 2$ statistics for categorical variables and ANOVA analyses for continuous variables. Significant numbers are in bold. * $p < .01$ ** $p <. .05$

***Processing speed***

For the composite z-score for processing speed, OABD showed the most impairments when compared to HC in both model 1 and 2 (β = -.34, $p$ <.01 and β = -.32, $p$ <.01), and more impairments than LDD in both model 1 and 2 (β = -.31, $p$ <.01 and β = -.34, $p$ <.01).

***Interference inhibition score***

The difference in interference inhibition score between OABD and HC was significant in both model 1 (β = -.22, $p$ <.01) and 2 (β = -.19, $p$ <.01). When comparing OABD patients with LLD patients, no significant differences were found in both model 1 (β = -.06, $p$ =.30) and 2 (β = -.09, $p$ = .12).



***Working memory***

For the composite z-score for working memory, the difference between OABD and HC in model 1 appeared significant (β = .18, $p$ <.01), and remained significant after adding the number of depressive symptoms in model 2 (β = .13, $p$ = .02). For the composite z-score for working memory, the difference between OABD and LLD in model 1 appeared significant (β = .16, $p$ <.01) and remained significant after adding depressive symptoms in model 2 (β = .23, $p$ < .01).

***Post-hoc analyses***

Because of the possibility of cognitive functioning being associated with somatic diseases[37,38], medication use[39,40,10] and disease duration[20,41], we conducted post-hoc linear regression analyses. In the third model, the number of somatic diseases was included. In model 4, the different types of medication were individually included (benzodiazepines, lithium, TCA, and SSRI) and in the fifth model, the duration of disease was included. All models were controlled for age, gender and level of education. Overall, these results were similar to the original analyses, suggesting that the difference in cognitive functioning between OABD, LLD and HC cannot be fully explained by these factors.

**Table 2:** Results of regression analyses between OABD, LLD and HC

| | LLD | | HC | |
|---|---|---|---|---|
| | **β** | ***p*** | **β** | ***p*** |
| **Episodic memory** | | | | |
| Immediate recall | | | | |
| Model 1 | .23 | <.01** | .30 | <.01** |
| Model 2 | .26 | <.01** | .26 | <.01** |
| Delayed recall | | | | |
| Model 1 | .31 | <.01** | .24 | <.01** |
| Model 2 | .29 | <.01** | .25 | <.01** |
| Z-score | | | | |
| Model 1 | .35 | <.01** | .35 | <.01** |
| Model 2 | .37 | <.01** | .34 | <.01** |
| **Processing speed** | | | | |
| Card I | | | | |
| Model 1 | .32 | <.01** | .34 | <.01** |
| Model 2 | .34 | <.01** | .32 | <.01** |
| Card II | | | | |
| Model 1 | .27 | <.01** | .39 | <.01** |
| Model 2 | .33 | <.01** | .34 | <.01** |
| Z-score | | | | |
| Model 1 | -.31 | <.01** | -.34 | <.01** |
| Model 2 | -.34 | <.01** | -.32 | <.01** |
| **Interference inhibition** | | | | |
| Model 1 | -.06 | .30 | -.22 | <.01** |
| Model 2 | -.09 | .12 | -.19 | <.01** |
| **Working memory** | | | | |
| Digits forward | | | | |
| Model 1 | .11 | .05* | .13 | .02* |
| Model 2 | .18 | <.01** | .08 | .18 |
| Digits backward | | | | |
| Model 1 | .16 | <.01** | .18 | <.01** |
| Model 2 | .21 | <.01** | .21 | <.01** |
| Z-score | | | | |
| Model 1 | .16 | <.01* | .18 | <.01** |
| Model 2 | .23 | <.01** | .13 | .02* |

*Note.* LLD = Late life depression, OABD = older age bipolar disorder, HC = healthy controls
* p <.05, **< p <.01

## DISCUSSION

The aim of this study was to investigate differences in cognitive functioning in terms of affected domain and magnitude in a large sample of OABD patients, LLD patients and HC, and to investigate whether this cognitive dysfunction in these groups can be explained by the current depressive symptoms. Our findings show that OABD and LLD patients exhibit more cognitive dysfunction than HC, with OABD showing worst cognitive functioning on all cognitive domains, except for interference inhibition. These differences remained significant after controlling for the effect of depressive symptoms at the time of testing. The higher cognitive dysfunction in OABD can therefore not be fully explained by current depressive symptoms. This finding contributes to the growing body of research on cognitive functioning in late life affective disorders.



Our results are in line with earlier findings[24] that showed that OABD showed worse cognitive functioning compared to LLD patients and HC. Our findings do not suggest decreased cognitive functioning in different domains as compared to LLD (qualitative difference), but that cognitive dysfunction in OABD is more severe in magnitude albeit in the same domains as in LLD (quantitative difference). These differences remained significant after controlling for the severity of the depressive symptoms at the time of testing. Additionally, differences in somatic burden are not likely to be an explanation for these results, since the number of somatic diseases did not differ significantly between OABD and LLD. Alternatively, cognitive dysfunction might be more a result of other differences between the affective disorders. Therefore, several other disease mechanisms might be worth considering in the light of this hypothesis.

First, the neuroprogression hypothesis postulates that every mood episode is toxic to the brain and leads to cognitive decline in both BD and MDD[20,41]. However, studies in younger adult patients show that a greater neurotoxicity effect is produced by manic episodes, and this thus might have a long-term negative impact on the evolution of cognitive function in BD[42]. It has already been found in our DOBi-cohort that the number of both depression and mania episodes were weakly related to cognitive functioning[43]. In addition, it was demonstrated[44] that a higher number of manic episodes had a negative impact on working memory and visual memory at five years follow-up. Second, both BD and MDD have been associated with changes in genetics, systems of neurotransmitter and neurotrophic factors, neuroinflammation, autoimmunity, cytokines, stress axis activity, chronobiology, oxidative stress and mitochondrial dysfunctions, all having an impact on cognitive functioning[45,41]. These aspects might have more impact on BD as BD has been repeatedly associated with an earlier age of onset and longer disease duration[46,47,48]. However, in post-hoc analyses (results not shown) we found that disease duration alone could not explain differences in cognitive functioning between OABD

and LLLD Lastly, there may be an association between medication use and cognitive functioning. Medication use differed greatly in our sample, whereas OABD patients mostly used lithium and LLD mostly used benzodiazepines. Statements about the effect of medication on cognition cannot be made unambiguously. Studies on the effect of lithium on cognitive functioning show varying results[39,40]. A meta-analysis and systematic review reported that lithium may provide neuroprotection against dementia in older people with BD, whereas another review concluded that lithium has a negative effect on memory and speed of information processing in bipolar disorder. It was found that in LLD patients[10], TCA use was associated with poorer episodic memory, slower processing speed and poorer interference control. They also found that the use of SNRI's and benzodiazepines were associated with slower processing speed. However, in post-hoc analyses (results not shown) we also did not found an effect of medication use that could explain the differences in cognitive functioning in our three groups.

Cognitive functioning in OABD and LLD is presumably associated with (a combination of) the above-mentioned factors. However, it remains unclear what the exact role of these mechanisms is, and to what extent the differences in cognitive functioning between LLD and OABD can be explained by these mechanisms; it could be possible that the above-mentioned explanations are present in both BD and MDD, but are more prominent in BD with negative consequences for cognitive functioning. However, this should be studied extensively.

A major strength of the current study is that we were the first to include groups of this magnitude in order to compare cognitive functioning between OABD patients, LLD patients and HC. We used a neuropsychological test battery, in which multiple domains could be differentiated. Therefore, we could draw more detailed conclusions about cognitive functioning in different domains. Our study also has some limitations that should be noticed. Due to combining two cohort studies, we were not able to include essential variables, among which a great part of the explanations mentioned before, in order to explore the disease mechanisms that might play a part in cognitive functioning in these groups. In addition, the OABD patient group consisted of outpatients where our LLD group also consisted of patients receiving treatment from their general practitioner (36.1%). Our results may therefore give a distorted picture, since our LLD group was presumably more high-functioning. At last, patients with a low MMSE score (< 17) were excluded from both cohort studies. This have caused that the most cognitively impaired participants were not included in the analyses.

In conclusion, our results indicate that OABD and LLD patients show worse cognitive impairments than HC in all domains, except for the domain of interference inhibition. With OABD showing worst cognitive dysfunction. These impairments cannot be fully explained by their current depressive symptoms, therefore indicating that cognitive dysfunction in these groups is related with other disease mechanisms. In order to develop treatment programs to improve coping mechanisms for impaired cognition and prevent further impairment, more research is needed to investigate which aspects influence cognitive dysfunction in OABD and LLD. The question arises which combination of factors specifically contribute to cognitive impairment in these late-life affective disorders. Future research should be focused on disease characteristics, including neuroprogression, biomarkers and pathophysiological processes, somatic comorbidities and medication use and how these characteristics are associated with the complex concept of cognitive functioning in both OABD and LLD.

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# 4

# **PART II:** UNDERSTANDING

# CHAPTER 5

# The relationship between cognitive and social functioning in older patients with bipolar disorder

Melis Orhan, Nicole Korten, Max Stek, Hannie Comijs, Sigfried Schouws & Annemiek Dols

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## ABSTRACT

**Background:** Patients with bipolar disorder (BD) show specific cognitive impairments, especially in the domains of attention, executive functioning and memory. Social and occupational problems seem to exist in 30-60% of BD patients. This study analysed the relationship between cognitive and social functioning in older age BD (OABD) patients.

**Methods:** This study included 63 OABD patients (aged >60). Cognitive functioning was measured by an extensive neuropsychological assessment including global cognitive functioning, attention, learning and memory, executive functioning and verbal fluency. Social functioning, was obtained by clinical interview, including global social functioning, meaningful contacts and social participation. Linear regression analyses were conducted between cognitive performance and social functioning and the role of depression severity and disease duration was explored.

**Results:** Global social functioning, number of meaningful contacts and social participation were not interrelated. Global cognitive functioning, learning and memory and executive functioning were positively associated with global social functioning. No associations were found between cognitive functioning and social participation or meaningful contacts. Depression severity and disease duration were no effect modifiers.

**Discussion:** Global social functioning judged by the clinician was found to be independent of social functioning defined by the number of social contacts and social participation as reported by the patient. Global social functioning was related to cognitive functioning. An integrative treatment intervention including cognitive training and addressing social functioning may improve daily functioning in OABD patients.

# INTRODUCTION

Bipolar disorder (BD) is a chronic mental disorder that is characterized by repeated periods of depression and mania, alternating with complaint-free periods[1]. Although the number of BD patients seems to decline with age, still 8 – 10% of psychiatric inpatients over age 55-60 are diagnosed with BD[2]. Due to our aging society, the number of patients with older age BD (OABD) is growing. Studies suggest that OABD patients exhibit specific clinical characteristics, differing from adult BD patients[3]. More insight in OABD functioning will facilitate tailoring specific treatments for this group, resulting in better treatment outcomes and overall functioning.

Attention has recently risen for the cognitive and social aspects of recovery[4,5,6]. OABD patients show specific cognitive deficits[7,8,9], predominantly in the domains of attention, memory, executive functioning and verbal fluency[8].



Additionally, social and occupational adjustment problems seem to exist in 30-60% of BD patients, as shown by a review including several BD patients from different age groups[10]. Social functioning seems to fluctuate in parallel with changes in mood symptom severity[4], indicating that more depressive symptoms lead to more social dysfunction. Prior studies show that poor social functioning predicts a shorter time to relapse[11] and more depressive episodes[12]. Additionally, there might be a gap between clinical and functional outcomes in adult BD patients (age 15-75)[13]. This indicates that despite a reduction in clinical symptoms, patients might not be functioning on the expected level, with consequences for health-related quality of life and functioning[14]. Furthermore, age seems to be negatively associated with social functioning in adult BD patients, suggesting that OABD patients experience even more social dysfunction than younger BD patients[12].

Only a few studies examined the association between cognitive and social functioning in adult BD patients. In a small ($n$ = 15) study earlier conducted[15] (age $M$ = 39, $SD$ = 13; 2001), cognitive impairments in several domains were found. However, only verbal learning and executive functioning were correlated with lower social and occupational functioning. It was also found that a single measure of processing speed was significantly correlated with lower social functioning over a 12-month period in adult BD patients ($n$ = 33; age $M$ = 40.2, $SD$ = 6.2)[16]. In a larger study, social competence largely mediated the relationship between cognitive functioning and functional outcomes in adult BD patients ($n$ = 130; age range 18 - 80)[17]. In addition, cognitive functioning was directly related to social activities. An earlier study[14] pointed out that verbal memory best predicted psychosocial functioning in BD patients.

To our knowledge, the association between cognitive and social functioning in OABD was only studied once[18]. This study investigated the association between cognitive functioning and social functioning in OABD patients (age >60). In this study, OABD patients living in the same catchment area of the mental health institution as their peers with schizophrenia were included from the total cohort of Dutch Older Bipolars (DOBi). A significant association between global cognitive and global social functioning in OABD patients was found. In continuation of these results, the aim of this study is to further investigate the specific relationship between cognitive and social functioning in OABD patients. The current study differs on several aspects from previous research. To date, most research has been conducted among the younger adult patient population, where our focus will be on OABD patients (>60), considering the different aspects of social functioning including global social functioning, self-reported social participation and network size and various domains of cognitive functioning. Based on previous research we hypothesize that global cognitive functioning [18,17] and learning and memory and executive functioning [15,14] are positively associated with social functioning. Since previous research showed stronger associations between poor cognitive and poor social functioning in more severely depressed adult BD patients[6,4], we thereby hypothesize that the positive association between cognitive functioning and social functioning is stronger in OABD patients with more depressive symptoms and a longer disease duration.

# METHODS

## Study sample

For this study data were used from the DOBi study, conducted in 2012[19]. In short, in this study all older patients (aged 60 years and over) in contact with services between January 1, 2012 and December 31, 2012 were identified by a computerized search in the electronic record-keeping system of the Mental Health Organization (GGZ inGeest, Amsterdam, the Netherlands). Patients were screened for eligibility if they had any registered diagnosis that could indicate bipolar disorder. Inclusion was possible when patients were clinically diagnosed with bipolar I disorder (DSM-IV-TR: 296.00-.06, 296.40- .46, 296.50-.56, 296.60-.66, 296.7), bipolar II disorder (DSM-IV-TR: 296.89) or bipolar disorder not otherwise specified (DSM- IV-TR: 296.80). Medical records of all potential participants were screened by a psychiatrist for exclusion criteria, including not being able to give written informed consent, not being able to communicate in Dutch or English, mental retardation (IQ < 70), poor cognitive functioning (MMSE <18) or a highly unstable psychiatric condition. Included patients were asked by their psychiatrist or community psychiatric nurse to provide written consent for participation in the study. 114 patients were eligible for study inclusion. 13 patients were not

willing to provide consent or to participate in the study, resulting in 101 patients. 38 patients had no neuropsychological examination or complete social functioning scores available, resulting in a study sample of 63 patients for the current study. A flow chart of the study sample is presented in Figure 1. The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands.

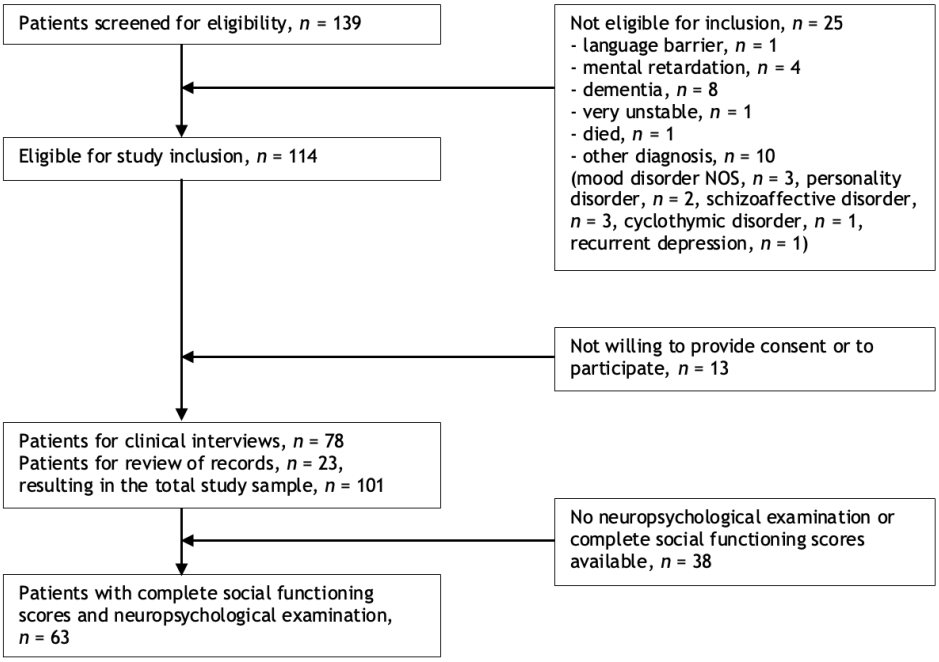


**Figure 1:** Flow chart of the DOBi study

## Measurements

### *Demographic characteristics*

Demographic data (e.g. age, sex, partner status, level of education) were obtained through interviews and then checked in patients' medical records. Education was divided into low, middle and high. Participants were labelled as low educated if only primary school or low-level high school was completed. Partner status was divided into having someone they considered as their permanent partner or not.

### *Clinical characteristics*

Diagnosis of bipolar disorder was confirmed by the Mini-International Neuropsychiatric Interview Plus (MINI[20]), which was performed by experienced clinicians. Duration of the disease (in years since first episode according to DSM-IV criteria) and age of onset were also obtained from the MINI interview. Number of admissions was obtained by interview. Current mania symptoms were assessed through the Young Mania Rating

Scale (YMRS[21]). The YMRS is scored on a scale from 0 to 60, with scores ≥ 12 indicating clinically relevant (hypo) mania. Current symptoms of depression were measured by the Center for Epidemiologic Studies Depression Scale (CES-D[22]). The CES-D is a self-report scale, consisting of 20 items. It measures depressive symptoms during the previous week, with scores ranging from 0 to 60. Scores ≥ 16 indicate clinically relevant depression.

***Social functioning***

Several measurements were conducted to assess social functioning. First, the Social and Occupational Functioning Assessment Scale (SOFAS[23]) was conducted to assess the level of global social functioning in the previous week, as estimated by patients' treating psychiatrist. The achieved score is a global rating of current social functioning ranging from 1 to 100, with lower scores indicating lower social functioning, and scores ≥ 90 suggesting no social impairments. Benchmarks are based on the quality of several areas concerning social functioning, such as containing personal hygiene, the quality of patients' contacts and occupational functioning. Second, the Social Participation Scale (SPS[24]) was used to measure self-report of involvement in 10 different social activities (e.g. doing groceries, doing sports or attending a church service). Possible answers are never, rarely or regularly. Higher scores indicate more regular participation in social activities. Third, patients' social network was assessed through the self-reported number of persons outside their household with whom they have regular and meaningful contact.

***Cognitive functioning***

Global cognitive functioning was assessed by the Mini Mental State Examination (MMSE[25]). In addition, subjects completed an extensive neuropsychological assessment, which involved tests on multiple cognitive domains as used in an earlier study[26], including:

- *Attention*: Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS-III[27]), Trail Making Test part A[28].
- *Learning and memory*: The 10 Words Test (learning – retention – recognition), a modified version of the Auditory Verbal Learning Test[29].
- *Executive functioning*: Trail Making Test part B[28], Modified version of the Stroop Color Word Test[30], Mazes (1 to 4) subtest of the Wechsler Intelligence Scale for Children (WISC[31]), and the Rule Shift Cards subtest of the Behavioral Assessment of the Dysexecutive Syndrome[32].
- *Verbal fluency*: Control Oral Word Association Test (COWAT[33]), Animal and Occupation Naming subtest of the Groningen Intelligence Test (GIT[34]).

Higher scores on the domains of attention and executive functioning indicate worse cognitive functioning and lower scores on the domains of learning and memory and verbal fluency indicate worse cognitive functioning.

***Statistical analysis***

Data were analysed using the Statistical Package of the Social Sciences (version 24.0, SPSS Inc., Chicago, IL, USA). First, descriptive analyses were performed for demographic and clinical characteristics, social functioning scores and cognitive functioning scores. Differences between the total cohort and the current study sample were calculated through t-tests for continuous variables or chi-square tests for categorical variables. A Mann-Whitney *U* test was used when the assumption of normality was not reached. For neuropsychological functioning, raw test scores were transformed into *z*-scores. The mean of these *z*-scores was used to compose functioning scores per cognitive domain. MMSE, SOFAS, SPS and CES-D scores were log transformed to obtain a near-normal distribution. To observe if the different social functioning measures were interrelated, Pearson's *r* has been conducted between the different aspects of social functioning. Separate regression analyses were conducted with the cognitive domains as independent variables and aspects of social functioning as dependent variables. Next, age, level of education and depressive symptoms will be entered as covariates.



The role of mood symptom severity (CES-D score) and disease duration was explored separately through the addition of an interaction-term with global cognitive functioning in the regression analysis that studied the association between global cognitive and global social functioning. When finding significant interaction effects ($p < 0.05$), stratified analyses will be conducted in the different groups. Results with a $p < 0.05$ will be regarded as statistically significant.

# RESULTS

### *Demographic and clinical characteristics*

The demographic and clinical characteristics of the patients with no neuropsychological data available (*N* = 38) and the study sample (*N* = 63) are summarized in Table 1. The median of the age of the participants in the study sample was 67 (IQR = 15) and gender was equally distributed. The majority of patients had children (73%). The median of the duration of the bipolar disorder was 38 years (IQR = 20) with an median of age of onset of 30 years (IQR = 24). Participants were not depressed or (hypo) manic at the time of testing as indicated by low YMRS scores (median = 3, IQR = 4) and low CES-D scores (median = 7, IQR = 15). To study possible selection bias we examined differences in demographic and clinical characteristics between the complete sample and the study sample. Patients that did not participate in the study sample were less likely to have a partner, and had less psychiatric admissions (Table 1).

**Table 1:** Descriptive variables (demographic, clinical, social and cognitive characteristics) of the total cohort and the study sample

| | **Total cohort (*N* = 101)** | **Study sample (*N* = 63)** | **Statistics: $X^2$ / t (df) *p*** |
|---|---|---|---|
| **Demographics** | | | |
| Age, *M* (*SD*) | 68.9 (7.8) | 67.9 (6.9) | 0.79 (162) .43 |
| Female, % (n) | 53.5 (54) | 49.2 (31) | 0.22 (1) .64 |
| Partner status, yes, % (n) | 55.7 (44) | 63.5 (40) | 4.76 (1) .03 |
| Children, yes, % (n) | 70.9 (56) | 73.0 (46) | 27.1 (1) <.01 |
| Pet, yes, % (n) | 26.9 (21) | 27.0 (17) | 30.0 (1) <.01 |
| Level of education, low, % (n) | 22.8 (18) | 19.0 (12) | 69.9 (3) <.01 |
| Place of residence, residential care, % (n) | 10.1 (8) | 6.4 (4) | 216.7 (2) <.01 |
| **Clinical characteristics** | | | |
| Age of onset, *M* (*SD*) | 33.0 (14.0) | 33.2 (15.8) | -0.06 (162) .95 |
| Duration of disease, *M* (*SD*) | 35.8 (13.6) | 34.7 (13.8) | 0.50 (162) .62 |
| Psychiatric admissions, *M* (*SD*) | 1.5 (3) | 2.2 (3.5) | -1.28 (162) .21 |
| YMRS, *M* (*SD*) | 5.2 (6.6) | 1.4 (4.6) | 3.94 (135.23) <.01 |
| CES-D, *M*( *SD*) | 11.1 (10.3) | 11.0 (10.6) | 0.03 (139) .98 |

**Table 1:** Continued

| | Total cohort (*N* = 101) | Study sample (*N* = 63) | Statistics: $X^2$ / t (df) *p* |
|---|---|---|---|
| **Social functioning** | | | |
| Social participation, median (IQR), range | 12 (4.3), 1 – 17 | 12 (4), 5 – 17 | MW .35 |
| SOFAS score, median (IQR), range | 65 (12), 35 – 85 | 65 (15) 35 – 85 | MW .18 |
| Meaningful contacts, % (n) | | | 103.13 (5) <.01 |
| 0-1 | 7.7 (6) | 4.8 (3) | |
| 2-5 | 41.0 (32) | 41.3 (26) | |
| 6 – 10 | 32.1 (25) | 30.2 (19) | |
| > 10 | 19.2 (15) | 28.3 (15) | |
| **Cognitive functioning** | | | |
| MMSE, median (IQR), range | 28 (3), 21 – 30 | 28 (2), 24 – 30 | MW .90 |
| Attention | | | |
| Digits forward, *M* (*SD*) | | 5.4 (1.2) | |
| Digits backward, *M* (*SD*) | | 3.9 (1.2) | |
| Trail Making Test part A (sec), *M* (*SD*) | | 60.6 (38.8) | |
| Learning and memory | | | |
| 10 Words test Learning (1-5), *M* (*SD*) | | 30.6 (8.3) | |
| 10 Words test Recall, *M* (*SD*) | | 4.7 (2.5) | |
| 10 Words test Recognition, *M* (*SD*) | | 18.0 (2.6) | |
| Executive functioning | | | |
| Trail Making Test part B, *M* (*SD*) | | 167.6 (130.7) | |
| Stroop test III* (line 1 – 4), *M* (*SD*) | | 59.1 (50.4) | |
| WISC Mazes (sec), *M* (*SD*) | | 147.5 (128.8) | |
| BADS Rule Shift Cards (score), *M* (*SD*) | | 2.9 (1.1) | |
| Verbal fluency | | | |
| D – A – T Letter fluency, *M* (*SD*) | | 27.6 (13.2) | |
| Animal Naming, *M* (*SD*) | | 20.6 (6.8) | |
| Occupational Naming, *M* (*SD*) | | 15.2 (5.9) | |

YMRS, Young Mania Rating Scale; CES-D, Center for Epidemiologics Studies Depression Scale; SOFAS: Social and Occupational Functioning Assessment Scale; MMSE: Mini Mental State Examination; n=the number of participants; M=mean; SD=standard deviation

Statistical tests were based on χ2 statistics for categorical variables and ANOVA analyses for continuous variables. Significant numbers are in bold.

* p < .01

** p <.05

### *Social functioning*

Social functioning scores are reported in Table 1. The median of the SOFAS of the study sample was 65 (IQR = 15), indicating that the study sample experienced moderate social impairments. The median of the Social Participation Scale was 12 (IQR = 4), suggesting that participants are involved at least on a regular basis in some of the 10 inquired activities (maximum score is 20). 30.2% of participants reported that they regularly have meaningful contact with 6 – 10 persons outside their household. No high correlations (all $r < .30$) were found between SOFAS scores, social participation and meaningful contacts, indicating that the measured aspects of social functioning are not highly interrelated.

### *Cognitive functioning*

Table 1 shows the scores on each cognitive domain. Most participants showed no global cognitive dysfunction as indicated by high MMSE scores (median = 28, IQR = 2).

### *Association between cognitive and social functioning*

The results from linear regression analyses between global cognitive functioning and global social functioning (SOFAS) appeared significant ($\beta = .37$, $p = .003$) and remained significant when controlling for the confounding variables age, level of education and depressive symptoms ($\beta = .31$, $p = .02$)(Table 2). Separate linear regression analyses were conducted to determine if the individual cognitive domains were associated with the several aspects of social functioning corrected for age, level of education and depressive symptoms (Table 2). The association between attention and global social functioning appeared significant ($\beta = -.30$, $p = .019$), but did not remain significant when adjusting for age, level of education and depressive symptoms ($\beta = -.257$, $p = .06$). Learning and memory showed a significant association with SOFAS scores as well ($\beta = .32$, $p = .011$) and remained significant when entering the confounding variables into the regression model. A significant association was also found for executive functioning ($\beta = -.47$, $p < .01$), which remained significant when entering the confounding variables into the regression model. Linear regression analysis between verbal fluency and global social functioning appeared significant ($\beta = .26$, $p = .04$), but did not remain significant when entering confounding variables into the regression model. When entering the confounding variables in a stepwise manner, attention and verbal fluency appear non-significant after entering CES-D score into the model.

The association between the cognitive domains, and respectively social participation and the number of meaningful contacts were not statistically significant (Table 2).

**Table 2:** The association between cognitive functioning and social functioning in older age bipolar patients with age, level of education and depressive symptoms as confounding variables

| | Social participation (log transformed) | | SOFAS score (log transformed) | | Meaningful contacts | |
|---|---|---|---|---|---|---|
| | β | *p* | β | *p* | β | *p* |
| MMSE (log transformed) | .15 | .26 | .31 | **.02** | -.07 | .60 |
| Attention | -.17 | .22 | -.25 | .06 | -.09 | .50 |
| Learning and memory | .24 | .11 | .33 | **.02** | -.10 | .53 |
| Executive functioning | .05 | .75 | -.53 | **<.01** | -.07 | .66 |
| Verbal fluency | .03 | .83 | .19 | .18 | .04 | .77 |

*Note.* Linear regression analyses were conducted with age, level of education and depressive symptoms as confounding variables. Independent variables and confounding variables were entered simultaneously into the regression model. OABD = Older age bipolar disorder; SOFAS = Social and Occupational Functioning Scale; MMSE = Mini Mental State Examination, β = standardized regression coefficient.



### *Mood symptom severity and disease duration in relation to cognitive and social functioning*

To explore the role of mood symptom severity and disease duration in the association between global cognitive functioning and the aspects of social functioning, interaction terms were entered in the regression models. None of the interaction-terms were statistically significant (all p>0.05).

## DISCUSSION

The aim of this study was to investigate the relationship between cognitive functioning and quantitative and qualitative measures of social functioning in OABD patients. We found a significant positive association between global cognitive and global social functioning as judged by the clinician. By looking closely into the different aspects of cognitive and social functioning, the domains learning and memory and executive functioning were found to be positively associated with global social functioning, whereas attention and verbal fluency were not. Cognitive functioning was not associated with social participation and the number of meaningful contacts as reported by the patients. Additionally, it was found that the different aspects of social functioning were not interrelated.

No associations were found between social participation and meaningful contacts and the several aspects of cognitive functioning. It was found earlier[17] that social activities were directly associated with cognitive functioning. This discrepancy in results could be explained by the fact that our measure of social participation was self-reported, where social activities in the earlier study[17] was observer-rated. We found significant

results between the SOFAS and cognitive functioning, where we did not find significant associations between social participation and meaningful contacts and cognitive functioning. As mentioned before, the SOFAS score is an estimate made by the treating psychiatrist, while social participation and meaningful contacts are self-reported. This discrepancy is supported by the finding that our measured aspects of social functioning appeared not to be highly interrelated, what indicates that we measured different aspects of social functioning. The SOFAS indicates if there are any problems in social functioning and focuses on the quality of social functioning in several areas, for example; maintaining personal hygiene, functioning in work and maintaining family and other interpersonal relations. Therefore, it is particularly an indication of the quality of social functioning. On the other hand, the social participation scale and the number of meaningful contacts are an indication of the quantity of social functioning. The social participation scale and the number of meaningful contacts do not indicate directly if there are any problems in patients' social functioning. For example, in the context of social participation; social services are highly available for the older adult population in the Netherlands. So despite experiencing cognitive impairments, it is still possible to participate in social activities. These findings might suggest that observer-rated measurements might be a better estimate of problems in social functioning that is not in line with self-reported aspects of social functioning. An additional option to improve the estimation of the quality of social functioning is to include qualitative self-report measurements, since social cognition is relatively preserved in adult bipolar patients[35].

Conforming our hypothesis and in line with findings in younger adult BD patients, our findings suggest that better global cognitive functioning is associated with better global social functioning in OABD. This is in line with our previous study[18]. In this study, a subset of OABD from the DOBi cohort was compared with their peers with schizophrenia living in the same catchment area using the same instruments to indicate global cognitive and global social functioning.

Contrary with our hypothesis, no significant interaction effects were found for symptom severity and disease duration. An explanation for this finding could be that YMRS and CES-D scores were relatively low in our study sample, indicating that the study sample was a relatively healthy group of patients with little or no mood symptoms at the time of testing. As mentioned before[4], it seems that psychosocial functioning fluctuates along with mood symptoms. This indicates that, since our study sample showed little or no mood symptoms at the time of testing, these psychosocial impairments might have been limited. With respect to the role of disease duration, previous results were mixed[6]. Our results suggest that disease duration does not interact in the association between cognitive and social functioning.

Besides finding an association between better global cognitive functioning and better global social functioning, we found that better learning and memory and better executive functioning were associated with better global social functioning. To our knowledge no other study has been conducted before focusing on the association between different aspects of cognitive and social functioning in the OABD patient population. However, our results are in line with prior publications in adult BD patients, where different studies found mixed results regarding the domains that have an association with cognitive functioning. An earlier study[14] compared a group of adult BD patients with high psychosocial functioning with a group of adult BD patients with low psychosocial functioning. It was found that verbal memory seemed to be a good predictor of social functioning in adult BD patients. Besides finding an association between verbal memory and social functioning, a group of adult BD patients was compared with healthy controls and also found an association between executive functioning and social functioning in adult BD patients[15]. Both studies did not take into account other cognitive domains, since scores on these domains did not differ between adult BD patients and the control group. However, in a meta-analysis conducted in adult BD patients[36], it was observed that all cognitive domains showed associations with global social functioning.



Our study has several strong points. In contrast to earlier studies, where functioning scores often consisted of limited number of measurements, we aimed to sketch a more complete view of both aspects of functioning by using more comprehensive measurements. This enhances the generalizability of our study results to real-world situations. To our knowledge no other study was conducted before focusing on the relationship between cognitive functioning and social functioning in the OABD patient population. Besides these strong points, there are some limitations that need to be acknowledged. First, our study we included participants that experienced little or no mood symptoms and little impairments in cognitive (MMSE <18) or social functioning, but hardly any potential participant was excluded for this criterion. However, as mentioned in the results section, a selection bias was present. These issues limit the generalizability of our results to most impaired patients. Thereby, a relatively small sample size and a cross-sectional study design were used, therefore we cannot make statements about the predictive value of the variables and studying potential moderators and mediators was limited.

Our results emphasize that better cognitive functioning is associated with better social functioning in OABD patients. These findings warrant specific clinical implications. When during the diagnostic process cognitive deficits are observed, it needs to be taken into account that these deficits can cause impairments in social functioning. Vice versa, when social impairments are observed, one should be alert on additional

cognitive deficits. The finding that the different aspects of social functioning are not interrelated stresses the need to include different aspects of social functioning in composing a reliable social functioning estimate.

In conclusion, our findings suggest that better functioning in learning and memory and executive functioning is associated with better global social functioning in OABD patients. For improving daily functioning in OABD patients, it seems of great importance to develop an integrative treatment program in which the quality of social and cognitive functioning is being addressed and improved. Suggestion for further research is to look into the association between cognitive and social functioning in a longitudinal study design to draw conclusions about the direction of the association between cognitive and social functioning in OABD patients and to study potential moderators and mediators.

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5

# CHAPTER 6

# The influence of social, psychological and cognitive factors on the clinical course in older patients with bipolar disorder

Melis Orhan, Janette Huijser, Nicole Korten, Nadine Paans, Eline Regeer, Caroline Sonnenberg, Patricia van Oppen, Max Stek, Ralph Kupka & Annemiek Dols

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## ABSTRACT

**Background:** Research on contributing factors in the clinical course of older adults with bipolar disorder (OABD) is sparse. Previous research showed that clinical factors (e.g. age of onset, lifetime psychotic features and suicide risk) were not associated with the course in OABD. In younger adults, worse social functioning, coping style, and worse cognitive functioning are found to be associated with an unfavourable course of bipolar disorder. Therefore, this study is focusing on social, psychological and cognitive factors in OABD. More insight in these factors is essential in order to develop and further specify preventive and treatment interventions in this group.

**Methods:** Data were used from the Dutch Older Bipolars (DOBi) cohort study. We included 64 patients for 3-year follow-up measurements, who were divided in a recurrent group and a non-recurrent group. Logistic regression analyses were conducted to assess associations between social, psychological, and cognitive factors, and non-recurrence.

**Results:** 39.1% reported at least one recurrence during the 3-year follow-up period. No significant associations were found between the social, psychological, and cognitive factors and having a recurrence during the follow-up period.

**Discussion:** In contrast to bipolar disorder in younger adults, social, psychological, and cognitive factors were not associated with the clinical course in OABD. Our results suggest that results from the adult BD population cannot be extrapolated to OABD patients, underlining the need for longitudinal studies in OABD.

# INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric disorder characterized by recurrent depressive episodes as well as manic, hypomanic, or mixed episodes[1]. Although the prevalence of BD seems to decline with age, a quarter of all patients with BD is over the age of 60[2.] It is expected that in the near future the number of older adults with BD (OABD) will increase significantly, due to our aging society. In comparison with BD in younger adults, OABD is more frequently characterized by progressive cognitive and overall functional impairment[3,4,1], leading to problems in occupational and social functioning. Most guidelines lack specific recommendations for OABD[5] and treatment strategies are mostly extrapolated from studies conducted in the younger adult BD population. The differences in characteristics between the adult BD and the OABD patient population may extent to the predictors of recurrence, urging for research in this area. However, research on contributing factors in the clinical course of OABD in order to develop and further specify treatment and preventive methods is sparse.

In a previous study conducted by our group, a three-year follow-up study design was used to investigate the association between multiple clinical predictors and their association with the clinical course of OABD. No associations were found between recurrence and possible clinical predictors such as physical illness, age at onset, onset polarity, and predominant polarity[6]. Whereas that study primarily focused on clinical and physical characteristics in the recurrence of mood episodes, studies in the adult BD population also stress the importance of social, psychological, and cognitive factors in the clinical course of BD. Findings in the adult BD population indicate that social factors contribute to the clinical course of BD. Poor social functioning and a lack of social support have been associated with a shorter time to relapse [7], more depressive recurrences[8] and a longer time to recover from mood episodes[9] in younger adult BD patients. Social functioning has been found to fluctuate in parallel with changes in mood symptom severity[10], suggesting that more mood symptoms lead to more social dysfunction. Having a partner at the onset of the illness was found to be associated with a better chance of achieving full inter-episodic recovery, compared to patients without a partner at the onset[11] . These factors may also play a role in the course of OABD.

Psychological factors such as coping style have also been marked as predictors of the clinical course in adult BD. Results from larger studies investigating the adult BD population showed that emotion-oriented and avoidance coping strategies are associated with more depressive recurrences[12] . In bipolar offspring, a passive-reactive coping strategy also increased the risk of mood episode onset and recurrent episodes[13].

Cognitive functioning was also found to be related with the clinical course in adult BD, with worse cognitive functioning being associated with a higher number of mood episodes, longer disease duration and more psychiatric admissions[14].

To date, treatment strategies for OABD are mostly based on predictors found in adult BD due to a lack of research in the OABD population. In order to develop additional treatment strategies for this specific group, the aim of this study is therefore to explore the role of social, psychological and cognitive factors in the clinical course of OABD. Factors that will be taken into account are based on associations found in the adult BD population, including global social functioning, social support, coping style, and cognitive functioning.

Our aim was to identify social, psychological, and cognitive factors associated with the clinical course in OABD. We hypothesized that worse social, psychological, and cognitive functioning, and a more passive coping style are associated with an unfavourable clinical course.

# METHODS

## Participants

Data were used from a dynamic cohort of OABD patients (Dutch Older Bipolars; DOBi). In short, in this longitudinal study we carried out a search of the computerized record-keeping system of a large mental health organization (GGZ inGeest, Amsterdam, the Netherlands), which identified 139 patients aged 60 years and older with a possible diagnosis of BD who had been in contact with mental health services between 1 January 2012 and 31 December 2012[15]. Patients were eligible for inclusion if they were clinically diagnosed with bipolar disorder I, bipolar disorder II or bipolar disorder not otherwise specified using a semi-structured diagnostic interview, the Mini International Neuropsychiatric Interview (MINI) Plus[16] Patients unable to provide informed consent due to an inability to communicate in either English or Dutch, mental retardation (IQ<70), poor cognitive functioning (MMSE < 18), or a highly unstable psychiatric condition were excluded[15]. 114 patients were eligible for inclusion, of which 13 were not willing to participate in the study. Of 101 patients, 78 provided written consent to complete baseline inclusion.

After 3 years, the records of the patients included at baseline were screened for follow-up: nine patients had died (causes of death: tumour, n=3; heart failure, n=2; delirium, n=1; lung failure, n=1; kidney failure, n=1; hip fracture, n=1), two were diagnosed with dementia and three were lost to follow-up. In total, 64 patients were willing to participate in follow-up measurements. The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands.

## Measurements

*Demographic characteristics*

Demographic data (e.g. age, sex, level of education) were obtained through face-to-face interviews and confirmed by checking the patients' medical records. Education was divided in low, middle, and high education groups.

***Clinical characteristics***

At baseline, the bipolar diagnosis (BD-I/BD-II/BD-NOS), number of manic and depressive episodes, number of admissions, and presence of lifetime psychotic features were derived from the MINI interview. Episode density is defined as total number of episodes divided by disease duration in years. The severity of affective symptoms at baseline was assessed in an interview using the Young Mania Rating Scale (YMRS[17]) and the Center for Epidemiologic Studies Depression Scale (CES-D[18]). The YMRS assesses current symptoms of (hypo)mania. Scores range from 0 to 60, with scores of ≥ 12 indicating clinically relevant (hypo)mania. The CES-D measures depressive symptoms during the previous week. Scores range from 0 to 60, with scores ≥ 16 indicating clinically relevant depression.



***Course of OABD***

Three years after baseline inclusion, patients were asked to participate in follow-up measurements. They were asked if they had experienced an episode in the past three years and if so, how many episodes they had experienced. The number of recurrences were checked in the patients' files. Participants were divided into a recurrent group and a non-recurrent group based on if they had experienced at least one recurrence during the 3-year follow-up or not.

***Social factors***

- Partner status: partner status was divided into having someone they considered as their permanent partner or not.
- Children status: it was noted if patients had children or not.
- Global social functioning: patients' treating psychiatrist estimated the level of global social functioning in the previous week, using the Social and Occupational Functioning Assessment Scale (SOFAS[1]). Scores on this scale range from 1 to 100, with higher scores indicating better social functioning and scores of ≥ 90 suggesting no social impairments.
- Social support: social support system of patients was assessed through the self-reported number of persons outside their household with whom they had a regular and meaningful contact. The group was divided into a group that had 0 – 5 meaningful contacts and a group that had more than 5 meaningful contacts.

***Psychological factors***

- Coping style: the Utrechtse Coping Lijst (UCL[19]) contains 47 items describing specific coping behaviour and measures the following seven coping strategies: active problem solving, palliative reaction, avoidance, seeking social support, passive reaction pattern, expression of emotions, and reassuring thoughts. Answers are on a 4-point likert scale ranging from 'seldom or never' to 'very frequently'. Active problem solving and comforting cognitions are thought to represent active coping styles, while avoidance, passive reaction, and expressing emotions are thought to reflect more passive coping styles. Palliative reaction and seeking social support are thought to reflect both passive and active coping styles[19]. The scores on the active coping styles were combined, as well as the scores on the passive coping styles. Higher scores represent higher levels of use of the concerning coping style.

***Cognitive factors***

Cognitive functioning: cognitive functioning was determined by a comprehensive battery of neuropsychological tests on several cognitive domains including:

- *Attention*: Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS-III[20]), Trail Making Test part A[21].
- *Learning and memory*: The 10 Words Test (learning – retention – recognition), a modified version of the Auditory Verbal Learning Test[22].
- *Executive functioning*: Trail Making Test part B[21], modified version of the Stroop Color Word Test[23], Mazes (1 to 4) subtest of the Wechsler Intelligence Scale for Children (WISC[24]), and the Rule Shift Cards subtest of the Behavioral Assessment of the Dysexecutive Syndrome[25].
- *Verbal fluency*: Control Oral Word Association Test (COWAT[26]), Animal and Occupation Naming subtest of the Groningen Intelligence Test (GIT[27]).

The overall cognitive functioning score was computed by summing the z-scores of all 13 tests. In addition, global cognitive functioning was assessed by the Mini Mental State Examination (MMSE[28]).

## Statistical analyses

Data were analysed using the Statistical Package of the Social Sciences (SPSS, version 25.0, SPSS Inc., Chicago, IL, USA). First, descriptive analyses were performed for demographic and clinical characteristics and for scores on the social, cognitive, and psychological factors. Differences between the recurrent group and the non-recurrent group were calculated through independent sample t-tests for continuous measures, chi-square tests for categorical variables, and Mann-Whitney U tests (MW) for variables that were not normally distributed. Before conducting logistic regression analyses, data was checked on multicollinearity by correlation analyses. When the correlation coefficient

was >.50, the variable was not included in the model. Separate logistic regression analyses were conducted between all social, psychological, and cognitive factors, and not having a recurrence during the follow-up period. In the first model, age and sex were added as possible confounders. In the second model, episode density was added as possible confounder. Results with a $p < 0.05$ were regarded as statistically significant.

## RESULTS

*Demographic and clinical characteristics*

N = 64 participants were included in follow-up measurements. Descriptive characteristics for both the recurrent and the non-recurrent group at baseline are summarized in Table 1. Participants in the non-recurrent group ($n = 39$, 60.9%) were significantly older than participants that experienced at least one recurrence during the three-year follow up ($p = 0.04$). Participants in the recurrent group were more often female ($p = 0.03$).

***Social factors***

The mean SOFAS score in the follow-up study sample was 65 (SD = 14). There was no significant difference in SOFAS score between the recurrent group and the non-recurrent group ($p = .11$). No significant difference was found in the number of meaningful contacts between the recurrent group and the non-recurrent group ($p = .66$). Fewer patients in the recurrent group had children ($p = 0.04$).

***Psychological factors***

No significant differences were found in coping style between the recurrent and the non-recurrent group.

***Cognitive factors***

No significant differences were found in global cognitive functioning or in the composite cognitive functioning score between the recurrent and the non-recurrent group.

***Course of OABD***

At follow up, 24 participants (37.5%) experienced one or more recurrences in the three years between baseline and follow-up: 18 participants (28.1%) had one recurrence, four participants (16.7%) had two recurrences, and one participant (1.6%) had three recurrences. Of all patients that experienced a recurrence, 11 participants (47.8%) experienced a predominant manic recurrence, 7 participants (30.4%) experienced a predominant depressive recurrence, 3 patients (13%) experienced a predominant mixed recurrence and the predominant polarity of 2 patients (8.7%) was unknown.

**Table 1:** Descriptive characteristics for the recurrence and non-recurrence group

| | Follow-up sample *N* = 64 | Recurrence *N* = 25 | Stable *N* = 39 | Statistics χ2 /t (df) or MW |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age, mean (SD), | 68.5 (9.6), 60.3 – 96.3 | 65.3 (4.6), 60.3 – 75.3 | 68.8 (8.4), 60.4 – 96.3 | 2.16 (60.75) .04* |
| Female, % (n) | 46.9 (30) | 64 (16) | 35.9 (14) | 6.06 (1) .01* |
| Partner, yes, % (n) | 59.4 (38) | 56 (14) | 61.5 (24) | 0.70 (1) .40 |
| Children, yes, % (n) | 67.2 (43) | 52 (13) | 76.9 (30) | 4.2 (1) .04* |
| Pets, yes % (n) | 23.4 (15) | 24 (6) | 23.1 (9) | 0.11 (1) .74 |
| Level of education, low, % (n) | 35.9 (23) | 28 (7) | 41 (16) | 4.3 (4) .56 |
| **Clinical characteristics** | | | | |
| DSM-IV-TR: bipolar I, % | 53.1 (34) | 60 (15) | 48.7 (19) | .32 (1) .57 |
| Age at onset, years, median (IQR), range | 13 (5), 8 – 64 | 29 (13.5), 10 – 61 | 36 (31), 8 – 64 | MW .03* |
| Mood episodes, median (IQR), range | 10 (16), 0 – 60 | 10 (16), 1 – 60 | 10 (17), 0 – 45 | MW .76 |
| Duration of disease, years, mean (SD), range | 34.8 (19), 1.3 – 79.3 | 36.5 (11.8), 2.4 – 50.7 | 33.2 (15.8), 1.3 – 79.3 | -.90 (62) 0.37 |
| Episode density, median (IQR), range | 0.3 (0.5), 0.1 – 1.6 | 0.31 (0.3), 0.1 – 1.4 | 0.33 (0.43), 0.1 – 1.6 | MW. .56 |
| CES-D, median (IQR), range | 13 (5), 4 – 33 | 13 (10), 8 – 30 | 13 (4), 4 – 33 | MW. .80 |
| YMRS, median (IQR), range | 3 (4), 0 – 27 | 1.5 (3.5), 0 – 27 | 3 (6), 0 – 25 | MW. .48 |
| **Social factors** | | | | |
| SOFAS score, mean (SD), range | 65 (14), 35 – 85 | 61 (11.2), 40 – 85 | 67.8 (11.1), 35 – 85 | 1.63 (62), .11 |

**Table 1:** Continued

| | Follow-up sample *N* = 64 | Recurrence *N* = 25 | Stable *N* = 39 | Statistics χ2 /t (df) or MW |
|---|---|---|---|---|
| **Psychological factors** | | | | |
| Cognitive functioning | 5.9 (18.8), -23.1 – 24.6 | 5.9 (25.6), -23.6 – 16.3 | 5.9 (13.7), -20.6 – 24.6 | MW .75 |
| Coping style, mean (SD) | | | | |
| Active coping style | 29.6 (5.2), 19 – 42 | 28.6 (5.8), 20 – 42 | 30.3 (4.9), 30.5 – 33.5 | 1.06 (45), .30 |
| Passive coping style | 35.0 (5.9), 24 – 49 | 36.7 (6.6), 27 – 49 | 33.8 (5.5), 24 – 47 | -1.54 (42), .15 |
| Experienced stigma, yes, % (n) | 57.8 (37) | 68 (167) | 51.3 (20) | 3.78 (1) .05* |

*Note.* YMRS, Young Mania Rating Scale; CES-D, Center for Epidemiologics Studies Depression Scale; SOFAS: Social and Occupational Functioning Assessment Scale; MMSE: Mini Mental State Examination; n=the number of participants; M=mean; SD=standard deviation; IQR=interquartile range; MW=Mann-Whitney U test; Episode density is defined as number of episodes divided by disease duration in years. Predominant polarity is defined as 50% of all mood episodes of a certain polarity depressive or manic

Statistical tests were based on χ2 statistics for categorical variables and t tests for continuous variables, and Mann-Whitney U tests in case of non-normal distributions, at a significance level of 5%. Significant numbers are in bold.

Results of the logistic regression analyses are presented in Table 2. When conducting individual logistic regression analyses for social, psychological and cognitive factors and non-recurrence in model 1, controlling for age and sex, no significant associations were found between SOFAS score, having children, the number of meaningful contacts, active coping style and passive coping style and non-recurrence.In model 2, episode density was added to the individual logistic regression analyses. No significant associations were found with SOFAS score, having children, the number of meaningful contacts, active coping style, and passive coping style, and non-recurrence.

**Table 2:** Results of analyses between non-recurrence and the psychological, social and cognitive factors in three models

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | **OR** | ***p*** | **OR** | ***p*** | **OR** | ***p*** |
| SOFAS score | .96 | .08 | .95 | .07 | .97 | .27 |
| Having children | .33 | .06 | .32 | .07 | .37 | .12 |
| Having a partner | .77 | .69 | .80 | .73 | 1.02 | .98 |
| Meaningful contacts | 1.70 | .31 | 1.66 | .34 | 3.15 | .08 |
| Cognitive functioning | .95 | .06 | .96 | .17 | .96 | .16 |
| Active coping | .95 | .39 | .95 | .46 | .95 | .44 |
| Passive coping | 1.08 | .15 | 1.10 | .11 | 1.07 | .26 |

*Note.* SOFAS: Social and Occupational Functioning Assessment Scale
In model 1, individual logistic regression analyses were conducted with age and sex as confounding variables. In model 2, individual logistic regression analyses were conducted with age, sex and episode density as confounding variables. In model 3, individual logistic regression analyses with age, sex and baseline mood.

# DISCUSSION

The results of our study suggest that participants in the recurrent group were younger, more often female, and less often had children. None of the other the investigated social, psychological, or cognitive factors were found to be associated with a differential prospective clinical course of OABD. Our results differ from findings in the younger adult BD population, suggesting that results from studies in younger adult population cannot be extrapolated to the OABD patient population.

In a previous study concerning the clinical course in OABD[6] found that no relevant clinical factors showed an association with recurrence in the 3-year follow-up period. As a consequence, we shifted our focus towards other factors that might be of greater importance. To the best of our knowledge, this is the first study addressing social, psychological, and cognitive factors in the course of OABD. Therefore, we cannot make

a priori statements concerning the OABD population. However, when looking at results from a study conducted in younger counterparts, it was found that female participants were observed to be at a greater risk for recurrence compared to male patients[29]. In line with these results, we found that participants in the recurrent group were more often female. Literature states that the relationship between children and well-being becomes more positive in older participants[30,31]. Amongst others, the role of children as a form of social support may become more important in the later stages of a person's life. In the general population, having non-residential children was also related to well-being and lack of depressive symptoms. This suggests that the finding of a previous finding of a negative link between children and well-being and mental health may not generalize to older people whose children have often left home already. The importance of children as caregivers and social contacts might prevail[32].

However, when looking at results from studies in older unipolar depressive patients, it was found that an unfavourable course of depression was associated with a younger age at onset of depression, a higher severity of depression, chronic pain, neuroticism, and loneliness[33]. It was also found that older age was an important risk factor for a poorer course in unipolar depression, and that this could not be explained by a range of well-established risk factors such as social network size and social support[34]. Whereas we found that participants in our recurrent group were younger, we did not take into account the other factors that were found to be significant in older unipolar depressive patients.



Whereas studies concerning the clinical course in OABD are sparse, several studies were conducted focusing on the clinical outcome in OABD. It has been found that the number of depressive symptoms was not associated with global social functioning[35]. Fewer depressive symptoms and better overall functioning were also associated with active coping in OABD, but more depressive symptoms were not found to be related to a more passive coping style[36]. Also active coping was associated with fewer depressive symptoms and better overall functioning in OABD patients, but more passive coping styles were not found to be related to more depressive symptoms[36].

Several strengths and limitations have to be taken into account when interpreting the results of our study. This was the first study investigating the contribution of social, psychological, and cognitive factors in the clinical course in OABD. To our knowledge, only one study[6] has been conducted in this area, and results failed to identify specific clinical predictors of the clinical course in OABD. Also, we have used a longitudinal study design to understand the direction of the associations with the possible predictors. Our study has several limitations. First, our goal was to explore multiple factors that could have an association with the clinical course of OABD. Our selection was based on predictors found in the younger adult BD population. Therefore, we may have not taken

into account all factors that might be of importance in OABD, such as loneliness and neuroticism, both of which appeared to be predictors of the course of the depression in elderly unipolar patients[29]. Second, some of the important predictors that we used were not assessed by standardized and valid measurement methods. Also, our study sample was relatively small. This might have caused an underestimation of the real associations due to a lack of statistical power.

Whereas we did not find any significant association between the social, psychological, and cognitive factors, and having a recurrence, we did find some significant differences between the recurrent and the non-recurrent group. It was found that participants in the recurrence group were younger, more often female, and fewer had children. We also found some statistical trends that might indicate the direction of results when studying these predictors in a larger sample. In model 1 with several demographic variables as confounders, a statistical trend was found between non-recurrence and better global social functioning (OR = 96, $p = .08$), between non-recurrence and having children (OR = .33, $p = .06$), and between non-recurrence and good cognitive functioning (OR = .95, $p = .06$). In model 2 with demographic variables and episode density as confounders, a statistical trend was found between non-recurrence and better SOFAS score (OR = .95, $p = .07$), and between non-recurrence and having children (OR = .32, $p = .07$).

In conclusion, our study indicates that the OABD population differs from the younger adult BD population, and that results from these adult BD patients cannot be extrapolated to OABD patients. The present study did not result in specific clinical implications, as none of the investigated social, psychological, and cognitive factors were associated with a differential clinical course of OABD. More research is needed in a larger sample to gain more insight in the factors associated with the clinical course of OABD to provide clinical guidance for the prevention of recurrence in OABD.

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6

# CHAPTER 7

# Psychiatric symptoms during the COVID-19 outbreak in older adults with bipolar disorder

Melis Orhan, Nicole Korten, Nadine Paans, Bodine de Walle, Ralph Kupka,
Patricia van Oppen, Almar Kok, Caroline Sonnenberg, Sigfried Schouws & Annemiek Dols

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## ABSTRACT

**Background:** Older adults with bipolar disorder (OABD) are vulnerable for a COVID-19 infection via multiple pathways. It is essential for OABD to adhere to the COVID-19 measures, with potential consequences for the psychiatric symptoms. This situation offers the unique opportunity to investigate factors of vulnerability and resilience that are associated with psychiatric symptoms in OABD.

**Methods:** This study included 81 OABD patients aged over 50 years. Factors measured at baseline in patients that participated in 2017/18 were compared with factors measured during the COVID-19 outbreak.

**Results:** Participants experienced less psychiatric symptoms during COVID-19 than (67.9% euthymic) than at baseline (40.7% euthymic). There was no difference in loneliness between COVID-19 and baseline. Not having children, more feelings of loneliness, lower mastery, passive coping style and neuroticism were associated with more psychiatric symptoms during COVID-19 measures.

**Discussion:** Participants experienced less psychiatric symptoms during COVID-19 measures when compared to baseline. Our results indicate promising targets for psychological interventions aimed at curing and preventing recurrence in OABD and improving quality of life in this growing vulnerable group.

# INTRODUCTION

The coronavirus disease (COVID-19) pandemic has quickly spread around the world thereby affecting many countries, including the Netherlands. As of March 17th 2020, the Dutch Government has introduced measures aimed at reducing the spread of COVID-19 in line with the World Health Organization: quarantine, social distancing and isolation of infected populations in order to contain the pandemic[1]. The course of COVID-19 is more serious and potentially fatal in older adults compared to younger adults and in those with somatic diseases, therefore these groups are considered "at risk". Older patients with a mental disorder belong to this risk group in terms of age, but also because of the frequent somatic comorbidity[2]. Therefore, it is essential for older patients with a mental disorder and their environment to adhere to the COVID-19 measures in order to prevent a COVID-19 infection.

It is expected that COVID-19 affects multiple health-related aspects directly and indirectly. Directly, COVID-19 infections may cause morbidity and mortality, and indirectly, the diminished access to healthcare facilities and long-term effects of social isolation and threat of COVID-19 may affect somatic and mental health. The COVID-19 measures have high psychological costs: they require adapting daily routines and may hamper social interactions that enhance health and quality of life and provide emotional support[3].



As seen in previous pandemics, the number of people who experience an increase in psychiatric symptoms is greater than the number of people directly affected by the disease itself. During a pandemic, individuals are exposed to uncertainty and fear for a longer period of time, resulting in a negative effect on mental health across the lifespan[4]. In addition, the COVID-19 measures are mostly aimed at limiting social contact. Social disconnection puts older adults, particularly those living alone, at a greater risk of isolation, seclusion, depression, and anxiety[5,6]. Vice versa, there is evidence that social support protects older individuals against harmful stress and promotes physical and emotional wellbeing[7,8,9].

In our naturalistic dynamic cohort including patients aged 50 years and over with a diagnosis of bipolar disorder (Dutch Older Bipolars (DOBi[10]), we have been studying characteristics in older adults with bipolar disorder (OABD). In previous studies conducted in the DOBi cohort, we did not find significant associations between several clinical, social, psychological and cognitive factors and recurrence[11,12]. Knowledge about factors that predict recurrence is essential in order to detect the most vulnerable patients, allocate resources for mental health services and develop specific treatment strategies. Due to COVID-19 measures, patients are at increased risk of recurrence of

psychiatric symptoms. Therefore, the aim of this study was to identify factors that are associated with psychiatric symptoms in OABD during COVID-19.

For this purpose, data from the DOBi study were used. Factors measured at baseline in patients that participated in 2017 and 2018 (baseline wave) were compared with measurements during the COVID-19 outbreak (COVID-19 wave). In the COVID-19 wave, patients with clinically relevant psychiatric symptoms were compared with euthymic patients on several aspects. Following this cohort in times of the pandemic and its associated measures offers the unique possibility to study the association between a life-event (the COVID-19 outbreak) and psychiatric symptoms, measures of vulnerability and resilience such as coping strategies, personality traits, social participation and social network. This will contribute to developing a treatment approach for this group that is vulnerable for recurrence at an older age[11], but for whom specific evidence-based recommendations are currently lacking[13].

Our hypothesis was that social isolation, a decline in social participation, more COVID-19-related concerns, a lower sense of mastery and more feelings of loneliness will increase psychiatric symptoms. In addition, we investigated the association between coping style, neuroticism and psychiatric symptoms. It was expected that a more passive coping style and more neuroticism were associated with more psychiatric symptoms.

# METHODS

## Study sample

Participants in the baseline wave had been included in the DOBi study in 2017 and 2018[10]. In short, all older patients (aged 50 years and over) in contact with services between January 1, 2017 and December 31, 2018 were identified by a computerized search in the electronic record-keeping system of the Mental Health Organization (GGZ inGeest, Amsterdam, the Netherlands). Patients were screened for eligibility if they had any registered diagnosis of bipolar disorder (BD), which was confirmed in the Mini International Neuropsychiatric Interview[14]. Medical records of all potential participants were screened by a psychiatrist for exclusion criteria, including: not being able to give written informed consent due to not being able to communicate in Dutch or English, IQ < 70, poor cognitive functioning (MMSE <18[15]) or a highly unstable psychiatric condition. Several questionnaires were conducted, assessing characteristics such as coping, personality, cognition and clinical characteristics. In the baseline wave, 130 participants were included in the study, and 106 of them gave permission on their informed consent to contact them for follow-up studies. In April 2020 (week 17), these 106 participants were contacted to participate in the COVID-19 wave, of whom 12

were not willing to participate, 1 had received a diagnosis of Alzheimer's disease, 4 had passed away and 8 were lost to follow-up. This resulted in a sample of 81 patients for the current study. DOBi was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands.

## Measurements

### *Demographic and psychiatric symptoms*

Demographic data (e.g. age, gender, partner status) were obtained through interviews in the COVID-19 wave. Psychiatric symptoms were measured in the baseline wave and COVID-19 wave, respectively with the Young Mania Rating Scale (YMRS[16]), with scores ≥ 12 indicating clinically relevant (hypo)mania, the Center for Epidemiologic Studies Depression Scale (CES-D[17]) with scores ≥ 16 indicating clinically relevant depression and the Beck Anxiety Inventory (BAI[18]). The BAI is a 21-item self-report instrument for measuring the severity of anxiety. Scores range from 0 to 63, whereby a score of 0 – 9 indicates normal or no anxiety, 10 – 18 mild to moderate anxiety, 19 – 29 moderate to severe anxiety and 30 – 63 severe anxiety.

### *Social functioning*

Several measurements were conducted to assess social functioning. First, the Social Participation Scale (SPS[19]) was measured in the baseline wave and the COVID-19 wave. The SPS was used to measure self-report of involvement in ten different social activities at baseline (e.g. doing groceries, doing sports or attending a church service). Higher scores indicate more frequent participation in social activities. We also calculated a social participation change score by subtracting social participation during COVID-19 from social participation at baseline. Patients' social network was measured in the COVID-19 wave. This was assessed by asking if participants have children and/or grandchildren and how their living situation (household composition) is during the COVID-19 measures. Third, feelings of loneliness were measured in the baseline wave and in the COVID-19 wave. Loneliness was measured by the Loneliness Scale[20]. The total loneliness score can be categorized into four levels with a score of 0 – 2 being not lonely, a score of 3 – 8 being moderately lonely, a score of 9 – 10 being severely lonely and a score of 11 being very severely lonely.



### *Mastery, coping and personality*

Mastery was measured in the COVID-19 wave. The Pearlin Mastery scale[21] measures the extent to which an individual regards their life chances as being under their personal control rather than fatalistically ruled. Coping style was measured in the baseline wave. Coping style was measured using the Utrechtse Copinglijst (UCL[22]). The subscales are divided into active and passive coping styles[22]. Personality traits were measured in the baseline wave, by the Revised NEO Personality Inventory (NEO-FFI[23]). In the present

study, we only included the 'Neuroticism'-scale, since neuroticism is a relatively well-established risk factor for depression and anxiety in older adults[24]. Since coping and personality are regarded as factors that are relatively stable over time, we used these factors measured in the baseline wave.

***COVID-19 related concerns***

COVID-19 related concerns were measured in the COVID-19 wave. Several multiple-choice questions were asked based on the study protocol as designed by an earlier study[25] thereby assessing if participants (or someone in their household) had been infected with COVID-19, how many hours they were spending inside their homes and which aspect of the COVID-19 outbreak was most concerning to them. In addition, a list of 20 multiple-choice questions asked for the perceived threat of the COVID-19 outbreak and how participants coped with the new situation. Based on a previous exploratory factor analysis in a large sample consisting of three Dutch psychiatric cohorts (n=1517), we computed three scales from the 20 items: "perceived COVID-19 mental health impact", "fear for the virus" and "positive coping". It was also assessed how participants were experiencing their mental health care and how this care was adapted due to COVID-19 measures. Furthermore, as suggested by an expert by experience (BdW), we added these open questions: "What do you experience as being the most disabling in this period?", "What are the positive aspects of this period?", "Are there any positive or negative life experiences that help you in this period?", "Are you supporting others in this period and in what manner are you doing that?". A complete and detailed overview of the items and their coding can be found elsewhere[29].

## Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (version 24.0; SPSS). First, descriptive analyses were performed for all study variables. Paired sample t-tests for continuous measures were conducted for normally distributed variables, and Wilcoxon Signed Rank tests (WS) were conducted for variables that were not normally distributed to investigate whether patient characteristics differed between the COVID-19 and baseline wave. Separate linear regression analyses were conducted with COVID-19 related concerns, social functioning, loneliness, mastery, coping style and neuroticism as independent variables and severity of depressive symptoms or anxiety symptoms as outcome measure. Due to the limited variability in mania scores, we decided not to include this variable in these analyses. In order to attain a normal distribution, severity of depressive symptoms and anxiety were log-transformed. Age and gender were entered as covariates. Additionally, with logistic regression analyses we studied differences in functioning between the symptomatic group and the euthymic group. The symptomatic group was defined by having psychiatric symptoms

above the cut-off score on minimally one of the three scales (CES-D ≥ 16, YMRS ≥ 12, BAI ≥ 19). Results with p < .05 were regarded as statistically significant.

## RESULTS

### *Descriptive statistics*

#### *Demographic and clinical characteristics*

In the COVID-19 wave, participants had a mean age of 66.1 (SD = 7.2), and 55.6 was female (Table 1). Only one participant (1.2%) was diagnosed with COVID-19 by a medical doctor. Of all participants, 49.4% was living alone, 50.6% had children and 32.1% also had grandchildren. On average, participants had few (hypo)manic symptoms (YMRS score, median = 0, IQR = 3), low depression scores (CES-D score, median = 8, IQR = 13.8) and low anxiety scores (BAI score, median = 6, IQR = 7). All scores were significantly lower than at baseline (YMRS and CES-D $p$ <.01, BAI p = .02). In the baseline wave, 40.7% of all participants was euthymic. A comparison between symptomatic participants in the baseline wave and in the COVID-19 wave is presented in Figure 1.

#### *Social functioning*

In the COVID-19 wave, participants had less social participation (median = 16, IQR = 3) than at baseline, (median = 24, IQR = 4, $p$ = <.01). Loneliness was moderate during COVID-19, with a median score of 3 (IQR = 4), with no significant difference compared to baseline (median = 3, IQR = 6).



#### *Factors associated with psychiatric symptoms during COVID-19*

Not having children ($B$ = -.23, $p$ = .03), experiencing more loneliness ($B$ = .08, $p$ < .01), lower mastery ($B$ = -.05, $p$ < .01), more passive coping ($B$ = .02, $p$ < .01) and higher neuroticism ($B$ = .10, $p$ = .05) were significantly associated with more severe depressive symptoms when controlling for age and gender. Regarding the COVID-19 related concerns, a significant association was found between more severe depressive symptoms and a higher perceived mental health impact ($B$ = .39, $p$ <.01), more fear for the virus ($B$ = .17, $p$ = .04) and less positive coping ($B$ = -.41, $p$ <.01). Having grandchildren ($B$ = -.14, $p$ = .23), the difference in social participation ($B$ = -.01, $p$ = .42) and active coping ($B$ = -.01, $p$ = .24) were not associated with depressive symptoms when controlling for age and gender.

More feelings of loneliness ($B$ = -.04, $p$ = .03), lower mastery ($B$ = -.03, $p$ < .01) and higher neuroticism ($B$ = .11, $p$ = .02) were significantly associated with more severe anxiety symptoms. Regarding the COVID-19 related factors, a significant association was found between a higher perceived mental health impact ($B$ = .26, $p$ <.01), more fear for the virus ($B$ = .17, $p$ = .04), less positive coping ($B$ = -.26, $p$ <.01) and more severe anxiety symptoms.

**Table 1:** Descriptive characteristics for the recurrent and non-recurrent group

| | Follow-up sample *N* = 64 | Recurrent *N* = 25 | Non-recurrent *N* = 39 | Statistics χ2 /t (df) or MW |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age, mean (SD), range | 67.4 (7.3), 60.3 – 96.3 | 65.3 (4.8), 60.3 – 75.3 | 68.8 (8.4), 60.4 – 96.3 | 2.16 (60.75), 0.04* |
| Female, % (n) | 46.9 (30) | 64 (16) | 35.9 (14) | 4.83 (1) .03* |
| Pets, yes % (n) | 23.4 (15) | 24 (6) | 23.1 (9) | 0.01 (1) .93 |
| Level of education, low, % (n) | 35.9 (23) | 28 (7) | 41 (16) | 3.67 (4) .45 |
| **Clinical characteristics** | | | | |
| DSM-IV-TR: bipolar I, % | 53.1 (34) | 60 (15) | 48.7 (19) | .78 (1) .38 |
| Age at onset, years, median (IQR), range | 30.5 (23.8), 8 – 64 | 29 (13.5), 10 – 61 | 36 (31), 8 – 64 | MW .09 |
| Previous mood episodes, median (IQR), range | 11 (15.2), 1 – 61 | 10 (16), 2 – 61 | 11 (17), 1 – 46 | MW .43 |
| Duration of disease, years, mean (SD), range | 34.5 (14.4), 1.3 – 79.3 | 36.5 (11.8), 2.4 – 50.7 | 33.2 (15.8), 1.3 – 79.3 | -.90 (62) .37 |
| Episode density, median (IQR), range | 0.3 (0.5), 0.1 – 1.6 | 0.31 (0.3), 0.1 – 1.4 | 0.33 (0.6), 0.1 – 1.6 | MW. .72 |
| CES-D, median (IQR), range | 13 (5), 4 – 33 | 13 (10), 8 – 30 | 13 (4), 4 – 33 | MW. .59 |
| YMRS, median (IQR), range | 3 (4), 0 – 27 | 1.5 (3.5), 0 – 27 | 3 (6), 0 – 25 | MW. .20 |
| Number of recurrences at follow-up, % (n) | | | | |
| One | - | 28.1 (18) | - | - |
| Two | - | 16.7 (4) | - | - |
| Three | - | 1 6 (1) | - | - |
| **Social factors** | | | | |
| Partner status, yes, % (n) | 59.4 (38) | 56 (14) | 61.5 (24) | 0.19 (1) .66 |
| Children, yes, % (n) | 67.2 (43) | 52 (13) | 76.9 (30) | 4.29 (1) .04* |
| SOFAS score, mean (SD), range | 65.9 (11.5), 35 – 85 | 63 (11.2), 40 – 85 | 67.8 (11.1), 35 – 85 | 1.63 (62), .11 |
| Meaningful contacts, >5, % (n) | 53.1 (34) | 44 (11) | 59 (11) | 0.19 (1) .66 |
| **Psychological factors** | | | | |
| Coping style, mean (SD) | | | | |
| Active coping style (UCL score) | 29.5 (5.3), 19 – 42 | 28.6 (5.8), 20 – 42 | 30.3 (4.9), 19 – 39 | 1.06 (45), .30 |
| Passive coping style (UCL score) | 35.0 (6.1), 24 – 49 | 36.7 (6.6), 27 – 49 | 33.8 (5.5), 24 – 47 | -1.54 (42), .13 |

**Table 1:** Continued

| | Follow-up sample *N* = 64 | Recurrent *N* = 25 | Non-recurrent *N* = 39 | Statistics χ2 /t (df) or MW |
|---|---|---|---|---|
| **Cognitive factors** | | | | |
| Global cognitive functioning (MMSE score) | 28 (3), 21 – 30 | 28 (2.5), 25 – 30 | 29 (3), 24 – 30 | MW .68 |
| Composite cognitive functioning score | 5.9 (18.8), -23.1 – 24.6 | 5.9 (25.6), -23.1 – 16.3 | 5.9 (13.7), -20.7 – 24.6 | MW .49 |

YMRS, Young Mania Rating Scale; CES-D, Center for Epidemiologics Studies Depression Scale; SOFAS: Social and Occupational Functioning Assessment Scale; MMSE: Mini Mental State Examination; UCL, Utrechtse Coping Lijst; n=the number of participants; M=mean; SD=standard deviation; IQR=interquartile range; MW=Mann-Whitney U test;
Episode density is defined as number of episodes divided by disease duration in years.

**Table 2:** Differences between the psychiatric symptomatic group and the euthymic group

| | Symptomatic | | Euthymic | | | |
|---|---|---|---|---|---|---|
| | **M** | **SD** | **M** | **SD** | **OR** | ***p*** |
| Age | 64.4 | 7.0 | 66.8 | 7.2 | .95 | .15 |
| Gender female, % n | 57.7 | 15 | 54.5 | 30 | 1.14 | .79 |
| Children yes, % n | 53.8 | 15 | 49.1 | 27 | .35 | .18 |
| Grandchildren yes, % n | 38.6 | 10 | 29.1 | 16 | 1.52 | .40 |
| Social participation difference, median IQR | 7 | 3.3 | 7 | 5 | 1.03 | .73 |
| Loneliness, median IQR | 5 | 3.3 | 2 | 3.5 | 1.49 | <.01** |
| Mastery | 19.8 | 4.8 | 25.1 | 4.7 | 0.79 | <.01** |
| Active coping | 24.4 | 5.7 | 26.9 | 4.7 | .90 | .07 |
| Passive coping | 44.6 | 4.8 | 42.8 | 7.1 | 1.04 | .29 |
| Neuroticism | 6.1 | 1.0 | 5.6 | 1.2 | 1.38 | .20 |
| Corona-related variables | | | | | | |
| Mental health impact | 2.8 | 0.7 | 2.1 | 0.6 | 6.71 | <.01** |
| Fear for the virus | 3.3 | 0.6 | 2.7 | 0.6 | 5.50 | <.01** |
| Positive coping | 3.3 | 0.5 | 3.8 | 0.5 | .17 | <.01** |

*Note.* Statistical tests were based on logistic regressions. M = mean, SD = standard deviation, IQR = interquartile range, OR = Odds ratio.
* p <.05
** p <.01

Having children (*B* = -.10, *p* = .32), having grandchildren (*B* = -.02, *p* = .88), difference in social participation (*B* = -.01, *p* = .53), active coping (*B* = -.02, *p* = .05) and passive coping (*B* = .02, *p* = .09) were not associated with more severe anxiety symptoms.

***Euthymic mood versus psychiatric symptoms***

Twenty-six participants were symptomatic, defined by CES-D ≥ 16 and/or YMRS ≥ 12 and/or BAI ≥ 19. Fifty-five participants were euthymic (Table 2). Participants in the symptomatic group had significantly higher loneliness scores ($p$ <.01, $OR$ = 1.49) and significantly lower levels of mastery ($p$ <.01, $OR$ = 1.26). Regarding the COVID-19 related concerns, participants in the symptomatic group also showed higher scores on the perceived mental health impact scale ($p$ <.01, $OR$ = 6.71), had more fear for the virus ($p$ <.01, $OR$ = 5.50) and used less positive coping ($p$ <.01, $OR$ = .17). No significant differences were found in age, gender, having children, having grandchildren, living situation, difference in social participation, coping style and neuroticism.

## DISCUSSION

To our knowledge, this is the first study that examined factors associated with psychiatric symptoms in OABD during the COVID-19 pandemic. The aim of this study was to identify factors of vulnerability and resilience in OABD, by investigating the relationship between multiple factors and psychiatric symptoms during COVID-19 measures ordained by the government. We found that our sample experienced fewer psychiatric symptoms during the first months of the COVID-19 outbreak than at baseline. We also found that not having children, more feelings of loneliness, lower mastery, a more passive coping style and higher neuroticism were associated with more severe depressive symptoms during COVID-19 measures. We also found a significant association between more feelings of loneliness, lower mastery, higher neuroticism and more severe anxiety symptoms during COVID-19 measures. Regarding the COVID-19 related concerns, we found that a higher perceived mental health impact, more fear for the virus and less positive coping were associated with more severe depressive and anxiety symptoms.

Contrary to our hypothesis, we found that our sample experienced less mental health related symptoms during COVID-19 when compared with measurements at baseline. Due to the actuality of this topic, available literature is sparse. However, when looking at younger adults with a pre-existing affective disorder, it was found that during the COVID-19 outbreak there was a heightened level of depression, anxiety, stress and general distress in the group of adults with a pre-existing affective disorder when compared to those without a mental disorder[26]. They also found that anxiety was even further elevated in respondents with bipolar disorder compared with those with depressive disorder. More in general, previous studies reported that life events characterized by disruption of daily routines are associated with the onset of depression and mania in adults[27,28]. An explanation for this discrepancy between younger patients and our results in older adults can be found in the maturation-hypothesis, stating that older adults may be less reactive to stressful events. According to the inoculation-hypothesis, it might be easier for older adults to cope with current stressful events, because they may have had to deal with similar stressors earlier in life[29,30].



An interesting finding in our study was that mania symptoms during the COVID-19 outbreak were relatively low, whereas it could be expected that changes in social rhythms would lead to more mania symptoms. Evidence shows that life events leading to social disruption were associated with the onset of manic but not with depressive episodes[31]. In our sample, we only included older patients and therefore hypothesize that the social rhythms in older patients might be less susceptible for the changes in daily life due to the COVID-19 measures. Overall, healthy older individuals have been

repeatedly shown to display higher social rhythm regularity than younger adults[32,33]. Moreover, the social isolation may result in an environment with lesser stressors and thereby reduce the onset of manic symptoms. Older adults are to a lesser extent dependent on external factors, such as a job or a more extensive family life, that determine their daily structure and thus social rhythm. Therefore, we hypothesize that COVID-19 measures do not have an evenly heavy impact on the daily activities of participants in our sample, when compared with the impact of the COVID-19 measures on the lives of younger adults or older patients who do not experience mental disorders. Also, data was collected when the COVID-19 measures were just recently implemented and that an increase in symptoms is expected to occur after a longer period.

More feelings of loneliness were associated with more severe depressive and anxiety symptoms. However, we did not find a difference between euthymic and psychiatric symptomatic participants in quantitative measurements of social functioning, such as social participation, having children, having grandchildren and living situation. This stresses the finding that the quality of social functioning is highly important and is not directly related with the quantity of social functioning, in line with our previous findings[34].

A higher level of neuroticism appeared to be related with more psychiatric symptoms, and a more passive coping style was related with more severe depressive symptoms but not with more severe anxiety symptoms. OABD have more passive coping styles[35], whereas active coping might prevent patients with BD from becoming more impaired in functioning and having psychiatric symptoms in later stages of the illness[36]. We did not find an association with active coping and the severity of depressive symptoms. This is not in line with previous findings in our cohort, that showed that a more active coping style was associated with less severe depressive symptoms[37]. An explanation for this discrepancy in results could be the fact that we compared current psychiatric symptoms, during the COVID-19 outbreak, with coping styles measured at baseline. It may be that due to the COVID-19 measures, certain coping behaviors like active coping, avoidance and seeking social support, had become unavailable or shifted to a different form. This has clinical implications as baseline passive coping was associated with more severe depressive symptoms and active coping may not be possible during the COVID-19 measures.

In line with our hypothesis, we found that lower mastery was associated with more mental health related symptoms. When looking at the role of mastery in late-life depression, higher mastery seems to facilitate adaptation under stressful events[38,39]. Moreover, mastery has a strong effect on the course of depression in later life and high mastery was identified as a significant predictor of recovery[40]. Therefore, mastery could be an important target for treatment, when applying cognitive behavioral

therapy (CBT) in OABD. Current guidelines emphasize the use of CBT as one of the psychological interventions in the treatment of BD in addition to psycho-education[41,42,43] A strong point in our study is that we were able to compare data collected during the COVID-19 measures with data collected pre-COVID. This comparison provides unique information about factors that play a role in psychiatric symptoms in OABD patients. Still, an important limitation of the current study is that we did not collect data during the period between baseline and measurements during the COVID-19 outbreak. For this reason, it cannot be excluded that other factors that occurred during the three years between baseline and measurements during COVID-19, have had an impact on current psychiatric symptoms. The severity of psychiatric symptoms at the time of inclusion at baseline is therefore also of great importance. Most participants were in contact with services since their inclusion at baseline, therefore it cannot be ruled out that the decrease in psychiatric symptoms is caused by enhanced care provision, e.g. a change in medication use. This also causes that we cannot make statements about the generalizability of our results to the non-COVID-19 situation. Our measurements were conducted a short period of time after the start of the pandemic, thus it should be stressed that our findings might not reflect the long term effects of the COVID-19 outbreak. We also have to take into account that the sample that we used was relatively small, especially for the number of analyses that we have conducted. This increases the risk that our findings are attributed to chance findings.



Our findings warrant specific clinical implications since we found that the COVID-19 related concerns were highly associated with psychiatric symptoms. Therefore, clinicians need to be aware of the impact of these concerns and these should be regarded as important targets in treatment during the COVID-19 measures. Moreover, psychiatric symptoms can increase because patients are not able to use the most adequate coping strategies due to the restrictions caused by the COVID-19 preventive measures. Repeated assessments to follow the possible development of psychiatric symptoms as a result of the prolonged COVID-19 measures are warranted. Future research may repeat the measures conducted during COVID-19 when the COVID-19 measures are no longer applicable, in order to make statements if the associations that we found are generalizable to the non-COVID-19 situation.

In conclusion, the current study provides unique information about factors of vulnerability and resilience that are associated with psychiatric symptoms in OABD. Whereas earlier studies failed in identifying factors that play a role in the recurrence of these symptoms, this study points out that loneliness, lower levels of mastery, passive coping and neuroticism play a significant role in the severity of psychiatric symptoms during the COVID-19 pandemic. Our study also provided important information about the burden of psychiatric symptoms in OABD during COVID-19. These aspects indicate

promising targets for psychological interventions aimed at curing and preventing recurrence in OABD and improve quality of life in this growing vulnerable group.

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# CHAPTER 8

# The course of psychiatric symptoms in older age bipolar disorder during the COVID-19 pandemic

Melis Orhan, Nicole Korten, Almar Kok, Dore Loef, Ralph Kupka, Sigfried Schouws, Patricia van Oppen & Annemiek Dols

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## ABSTRACT

**Background:** The COVID-19 pandemic gives us the unique opportunity to study the course of psychiatric symptoms in older adults with bipolar disorder (OABD) whilst experiencing a collective long lasting stressor. The aim of this study was to investigate the course of depressive, manic and anxiety symptoms in OABD during the first six months of COVID-19 and how loneliness and mastery are associated with this course. Mastery is defined as the control one experiences over one's life and environment. Resilience is defined as adaptation to challenging life conditions encompassing several aspects of personal resources.

**Methods:** In April 2020 (n = 81), June 2020 (n = 66) and September 2020 (n = 51), participants were included from the Dutch Older Bipolars (DOBi) cohort study.

**Results:** Depressive, manic and anxiety symptoms increased over all timepoints. Participants with a higher sense of mastery experienced a greater increase in depressive and anxiety symptoms. Loneliness did not interact with the course of these symptoms.

**Discussion:** OABD were resilient in the first months of COVID-19 outbreak, depressive, manic and anxiety symptoms increased as the pandemic continued. Treatment strategies in coping with long lasting stressful events should include the focus on sense of mastery.

# INTRODUCTION

As of the beginning of 2020, the world is suffering from a global pandemic due to the outbreak of coronavirus SARS-CoV-2 (COVID-19). To reduce the spread of this virus, local governments set up measures, varying in strictness and timing. Restriction measures as proposed by the World Health Organization[1] included staying at home as much as possible, prohibiting group activities, and closing many public facilities. Because older people were regarded as the group most at risk for suffering severely of COVID-19 outcomes, visiting them was discouraged and for many, professional health care was halted or limited. In the first year of the COVID-19 outbreak, no vaccine was available, thus these measures were strictly maintained in order to reduce the spread of the virus and to protect the most vulnerable groups in our society. Studies that investigated the effects of the COVID-19 outbreak show greater psychological distress in psychiatric patients when compared with healthy controls[2]. However, when symptom levels in psychiatric patients were compared before and during the first months of the COVID-19 outbreak, changes were minimal or even negative in individuals with severe and chronic mental health disorders[3, 4].

Several studies reported younger age as a risk factor for mental health problems amid COVID-19 in the general population[5, 6]. However, it was also found in the general population that mental health problems during the COVID-19 outbreak were more prevalent among older adults[7]. In community dwelling older people in the Netherlands, loneliness increased in the first two months after the implementation of the COVID-19 measures, while there was no difference in depressive and anxiety symptoms[8]. Notably, personal losses, concerns about the pandemic, and a declined trust in societal institutions were associated with increasing mental health problems and emotional loneliness and not the frequency of social contacts[8]. Loneliness can be defined as the evaluation of a discrepancy between the desired and the achieved network of relationships as a negative experience[9]. It is therefore an important target for interventions, especially during the COVID-19 outbreak, since social isolation and loneliness increase older adults' risk for anxiety, depression, cognitive dysfunction, heart disease and mortality[10].



Since both an older age and pre-existing health problems are found to be risk factors for an increase in mental health symptoms during the COVID-19 pandemic, older adults with bipolar disorder (OABD) are particularly vulnerable for a decrease in wellbeing. However, a study conducted in younger adult patients with bipolar disorder (BD) also showed an initial increase of manic symptoms[11]. Nevertheless, in the study that we have conducted in April 2020, in the beginning of the COVID-19 pandemic, we found in our cohort of OABD, that they showed less depressive, manic and anxiety symptoms

in the first month of the COVID-19 pandemic, when compared to three years earlier[3]. This is in line with findings in community dwelling older people[8] and possibly a result of a 'pulling together effect' that can accompany an initial crisis[12]. Hereby, individuals undergoing a shared experience might support one another, thus strengthening social connectedness and decreasing mental health symptoms. However, in patients with higher loneliness and lower mastery we found more depressive and anxiety symptoms. Therefore, we decided to zoom in on these associations in current follow-up study. Mastery is defined as the sense of control one experiences over one's life and environment[13]. Mastery is also associated with resilience[14], which is defined as the dynamic process of adaptation to challenging life conditions encompassing several aspects of personal resources and is considered to be protective against mental disorders[15]. At this point, it remains unclear whether these patients also have a less favorable course of mental health symptoms during the COVID-19 pandemic. As this pandemic is a life-event that all patients are exposed to simultaneously, factors associated with recurrence of mental health symptoms during the COVID-19 outbreak may generalize to post-pandemic times and be identified as treatment targets.

The aim of this study was to investigate the course of depressive, manic and anxiety symptoms in OABD during the first six months of COVID-19 and how loneliness and mastery are associated with these symptoms. Our research questions are (1) what is the course of depressive, manic and anxiety symptoms during the first six months of the COVID-19 pandemic and (2) how are loneliness and mastery associated with the course of these symptoms during the COVID-19 pandemic? With the ongoing COVID-19 pandemic and associated measures, and thereby enduring exposure to a crisis environment and social isolation, we hypothesized that depressive, manic and anxiety symptoms will increase after the first months of the pandemic as the 'pulling together effect' fades off. We also hypothesize that participants who report more loneliness during the pandemic, will show a greater increase in depressive, manic and anxiety symptoms than participants who report less loneliness. In addition, we also hypothesize that participants that have a lower sense of mastery will show a greater increase in depressive, manic and anxiety symptoms.

# METHODS

## Study sample

Participants were recruited from the DOBi (Dutch Older Bipolars) cohort study. Participants had been included in the DOBi study in 2017 and 2018 (T0[16]). In brief, all patients aged 50 years and over in contact with services on January 1, 2017 were identified by a computerized search in the electronic record-keeping system of the Mental Health Organization (GGZ inGeest, Amsterdam, the Netherlands). Patients were screened for eligibility if they had any registered diagnosis of BD, which was confirmed in the Mini International Neuropsychiatric Interview[17]. Medical records of all potential participants were screened by a psychiatrist for exclusion criteria[16]. From the 130 Participants that were included in 2017 and 2018 (T0) 106 gave permission on their informed consent to contact them for follow-up studies (81.5%). Of these participants, 81 participated in April 2020, week 17 (T1), 66 participated in June 2020, week 25 (T2) and 51 participated in September 2020, week 39 (T3). Among all included participants, 50.6% participated in three evaluations, 37.3% participated in two evaluations and 12% participated in only one evaluation. Figure 1 shows the most important COVID-19 governmental measures, mortality rates, infections and hospital admissions on these dates in the Netherlands. DOBi was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands.

## Measurements

### *Demographics and mental health symptoms*

Demographic data (e.g. age, gender, partner status) were obtained through interviews at T0, T1, T2, and T3, see Table 1. Mental health symptoms were measured at T0, T1, T2, and T3, respectively with the Young Mania Rating Scale (YMRS[18]), with scores ranging from 0 to 60, and scores ≥ 12 indicating clinically relevant (hypo)mania, the Center for Epidemiologic Studies Depression Scale (CES-D[19]) with scores ranging from 0 to 60 and scores ≥ 16 indicating clinically relevant depression, and the Beck Anxiety Inventory (BAI[20]). The BAI is a 21-item self-report instrument for measuring the severity of anxiety; scores range from 0 to 63, whereby a score of 0 – 9 indicates normal or no anxiety, 10 – 18 mild to moderate anxiety, 19 – 29 moderate to severe anxiety and 30 – 63 severe anxiety.

### *Loneliness*

Feelings of loneliness were measured at T0, T1, T2, and T3. Loneliness was measured by the Loneliness Scale[21]. The scale has 11 items, with possible answers "yes", "more or less" and "no". The total loneliness score can be categorized into four levels with a score of 0 – 2 being not lonely, a score of 3 – 8 being moderately lonely, a score of 9 – 10 being severely lonely, and a score of 11 being very severely lonely.

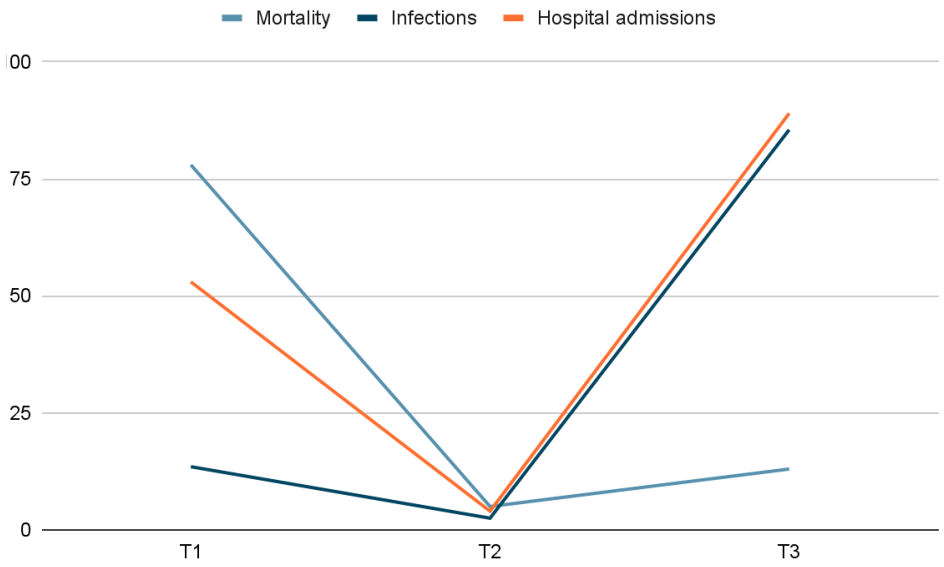


**Figure 1:** The number of hospital admissions and mortality during the COVID-19 pandemic in the Netherlands at T1, T2, and T3 (source: RIVM, 2021)

| Week 17 (29-04-2020) | Week 25 (21-06-2020) | Week 39 (27-09-2020) |
|---|---|---|
| - First lockdown<br>- Restaurants / bars are closed<br>- Everybody works from home<br>- Schools are closed<br>- Non-essential shops are closed | - Restaurants / bars are open<br>- Schools are open<br>- Contact professions can do their job | - 2 weeks before the second lockdown<br>- Restaurants / bars are partly closed |

*Note.* T1 = April 2020; T2 = June 2020; T3 = September 2020; source: www.rivm.nl

### *Mastery*

Mastery was measured at T1, T2, and T3. The Pearlin Mastery scale[13] measures the extent to which an individual regards their life chances as being under their personal control rather than fatalistically ruled. The scale has seven items, with answers on a 4-point Likert scale from "Strongly disagree (1)" to "Strongly agree (4)". Scores range from 7 to 24, with higher scores indicating a higher sense of mastery.

## Statistical analysis

Means and standard deviations were computed to describe our sample at T0, T1, T2 and T3. In order to assess the course of symptoms of depression, anxiety and mania during the COVID-19 pandemic (T1, T2 and T3), we used linear mixed models with random intercept to compare changes in these measurements during COVID-19. Adding a random slope did not improve the model, so adding this was omitted. For the regression analyses, missing data in depressive, manic and anxiety symptoms was

imputed following multiple imputation, using age at baseline and loneliness, mastery and psychiatric symptoms at all time points as predictors. Depressive, manic and anxiety were log-transformed in order to obtain a normal distribution. The models were estimated with random intercepts to account for the dependency in the data within individuals. We performed multiple independent linear-mixed effect models with depressive, manic and anxiety symptoms as dependent variables. The time points were dummy coded with T1 as comparator. Interaction effects were added to the model based on our earlier findings[3], with mastery and loneliness at T1 in separate models as main effect and interaction-effects, and age as confounding variable. Age was grand-mean centered in the analyses. Results with a $p < .05$ were regarded as statistically significant. Interaction-terms were considered statistically significant when $p < .10$.

# RESULTS

## Course of mental health symptoms during the COVID-19 pandemic

### Depressive symptoms

Figure 2 shows the course of mental health symptoms during the first six months of the COVID-19 pandemic, whereas Table 2 presents the values of the associations between loneliness and mastery and the course of depressive, anxiety and mania symptoms. There was no significant difference in depressive symptoms between T1 and T2 ($b = .17$, $t = 1.68$, $p = .10$) and between T2 and T3 ($b = .20$, $t = 1.86$, $p = .07$). However, there was an overall significant increase in depressive symptoms between T1 and T3 ($b = .37$, $t = 3.86$, $p < .01$).



#### *Anxiety symptoms*

Anxiety symptoms increased significantly between T1 and T2 ($b = .18$, $t = 2.05$, $p = .04$). We did not observe a significant difference in anxiety symptoms between T2 and T3 ($b = -.11$, $t = -.98$, $p = .33$) or between T1 and T3 ($b = .06$, $t = .60$, $p = .55$).

#### *Mania symptoms*

Mania symptoms did not increase between T1 and T2 ($b = -.08$, $t = -.75$, $p = .45$). At T3, mania symptoms were significantly higher than at T2 ($b = 1.17$, $t = 14.82$, $p < .01$) and T1. ($b = 1.09$, $t = 12.01$, $p < .01$).

**Table 1:** Psychiatric symptoms and social functioning at the different time points during the COVID-19 pandemic

| | T0 (n = 81) | T1 (n = 81) | T2 (n = 66) | T3 (n = 51) |
|---|---|---|---|---|
| Demographics | | | | |
| Age, M (SD) | - | 66.1 (7.2) | 66.4 (7.3) | 66.9 (6.8) |
| Gender, female % (n) | 55.6 (45) | 55.6 (45) | 50.8 (33) | 54 (27) |
| Living situation | | | | |
| Alone (%) | - | 49.4 | 51.5 | 44.0 |
| Children, yes % | - | 50.6 | 50.0 | 48.0 |
| Grandchildren, yes % | - | 32.1 | 30.3 | 32.0 |
| Psychiatric symptoms | | | | |
| YMRS, median (IQR) | 2 (4) | 0 (3) | 0 (2) | 6 (3) |
| Above cut-off, % | 1.2 (1) | 1.2 (1) | 0 (0) | 0 (0) |
| CES-D, median (IQR) | 12 (16.5) | 8 (13.8) | 11.5 (19) | 13 (18) |
| Above cut-off, % (n) | 53.5 (37) | 26.2 (61) | 43.4 (38) | 59.2 (30) |
| BAI, median (IQR) | 7 (15.3) 0 - 63 | 5.5 (7) | 7 (12) | 6 (14) |
| Above cut-off, % (n) | 47.1 (32) | 22.5 (18) | 43.9 (29) | 27.3 (14) |
| Social functioning | | | | |
| Social participation M (SD) | 23.4 (3.6) | 16.6 (2.4) | 19.2 (3.0) | 20 (3.1) |
| Loneliness M (SD) | 3 (6) | 3 (4) | 3.9 (3.2) | 4.5 (3.2) |
| Mastery M (SD) | - | 19.1 (5.2) | 19.1 (5.1) | 18 (8) |
| COVID-19 related factors | | | | |
| COVID-19 infection, yes % (n) | - | 1.2 (1) | 1.5 (1) | 3.9 (2) |
| Mental health impact, M (SD) | - | 2.3 (0.8) | 2.4 (0.8) | 2.4 (0.7) |
| Fear for the virus, M (SD) | - | 2.9 (0.6) | 2.8 (0.7) | 2.9 (0.6) |
| Positive coping, M (SD) | - | 3.6 (0.6) | 3.6 (0.7) | 3.5 (0.6) |

*Note.* T1 = April 2020, T2 = June 2020, T3 = September 2020.
Abbreviations: YMRS, Young Mania Rating Scale; CES-D, Center for Epidemiologic Studies Depression Scale; BAI, Beck Anxiety Inventory; IQR, interquartile range; M, mean; SD, standard deviation.

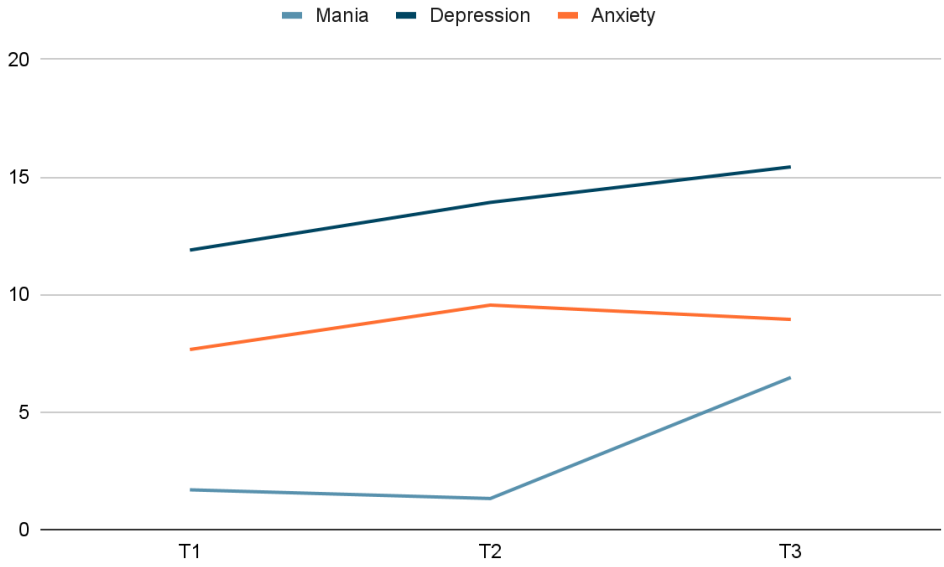


**Figure 2:** The course of psychiatric symptoms during the COVID-19 pandemic at T1, T2 and T3

*Note*. T1 = April 2020, T2 = June 2020, T3 = September 2020. Depressive symptoms T1 = T2, T2 = T3, T1 < T3. Anxiety symptoms T1 < T2, T2 = T3, T1 = T3. Mania symptoms T1 = T2, T2 < T3, T1 < T3

### *Effect of mastery and loneliness on the course of mental health symptoms*

In Table 2 the interaction effects for mastery and loneliness on the course of the different mental health symptoms are shown. In Figure 3 the significant interaction effects for mastery on the course of the different mental health symptoms are displayed.



### *The effect of mastery and loneliness on depressive symptoms*

Between T1 and T2, the interaction effect for mastery and depressive symptoms was significant ($b$ = .68, $p$ <.01). Participants with a higher sense of mastery showed a greater increase in depressive symptoms than participants with a lower sense of mastery. Between T2 and T3, this effect faded ($b$ = -.34, $p$ = .11). Participants with higher mastery had lower levels of depression on each timepoint.

We did not find a significant interaction effect for loneliness between all the time points.

**Table 2:** Results of the linear mixed model analyses between different timepoints and psychiatric symptoms

| | **Depressive symptoms (log-transformed)** | | | **Anxiety symptoms (log-transformed)** | | | **Mania symptoms (log-transformed)** | | |
|---|---|---|---|---|---|---|---|---|---|
| Slope | Estimate | Std Error | p-value | Estimate | Std Error | p-value | Estimate | Std Error | p-value |
| T1-T2 | .17 | .10 | .10 | .18 | .09 | **.04*** | -.08 | .10 | .45 |
| T1-T2 * mastery | .68 | .20 | **<.01**** | .59 | .17 | **<.01**** | .21 | .21 | .33 |
| T1-T2 * loneliness | -.12 | .21 | .57 | .20 | .18 | .26 | -.14 | .21 | .51 |
| T2-T3 | .20 | .11 | .07 | -.11 | .12 | .33 | 1.17 | .08 | **<.01**** |
| T2-T3 * mastery | -.34 | .21 | .11 | -.22 | .24 | .35 | -.19 | .16 | .23 |
| T2-T3 * loneliness | -.17 | .21 | .41 | -.25 | .24 | .29 | .32 | .16 | **.05*** |
| T1-T3 | .37 | .10 | **<.01**** | .06 | .10 | .55 | 1.09 | .09 | **<.01**** |
| T1-T3 * mastery | .35 | .19 | .06 | .37 | .21 | .08 | .01 | .19 | .94 |
| T1-T3 * loneliness | -.29 | .19 | .12 | -.05 | .21 | .80 | .18 | .18 | .32 |

*Notes:* T1 = April 2020, T2 = June 2020, T3 = September 2020.

***The effect of mastery and loneliness on anxiety symptoms***

When looking at anxiety symptoms, we found a significant interaction effect for mastery and anxiety symptoms between T1 and T2 ($b$ = .59, $p$ <.01), with participants with a higher sense of mastery showing a greater increase in anxiety symptoms than participants with a lower sense of mastery between T1 and T2. We did not observe a significant interaction effect for mastery between T2 and T3 ($b$ = -.22, $p$ = .35). This indicates that there was no difference in increase in anxiety symptoms between patients with a higher and participants with a lower sense of mastery between T2 and T3. Participants with higher mastery had lower levels of anxiety on each timepoint.

For loneliness, we did not find a significant interaction effect between all the time points.

***The effect of mastery and loneliness on mania symptoms***

We did not observe a significant interaction effect for the sense of mastery between T1 and T2 ($b$ = .23, $p$ = .33) and between T2 and T3 ($b$ = -.19, $p$ = .23). This indicates that there was no significant difference in the course of mania symptoms in participants with different levels of mastery. Participants with higher mastery had lower levels of mania on each timepoint.

We did not find a significant interaction effect for loneliness and the course of mania symptoms between T1 and T2, ($b$ = -.14, $p$ = .51), T1 and T3 ($b$ = .18, $p$ = .32). However, we did find a significant interaction effect for loneliness between T2 and T3 ($b$ = .32, $p$ = .05). This interaction effect indicates that participants who experience more loneliness also show a greater increase in mania symptoms between T2 and T3.

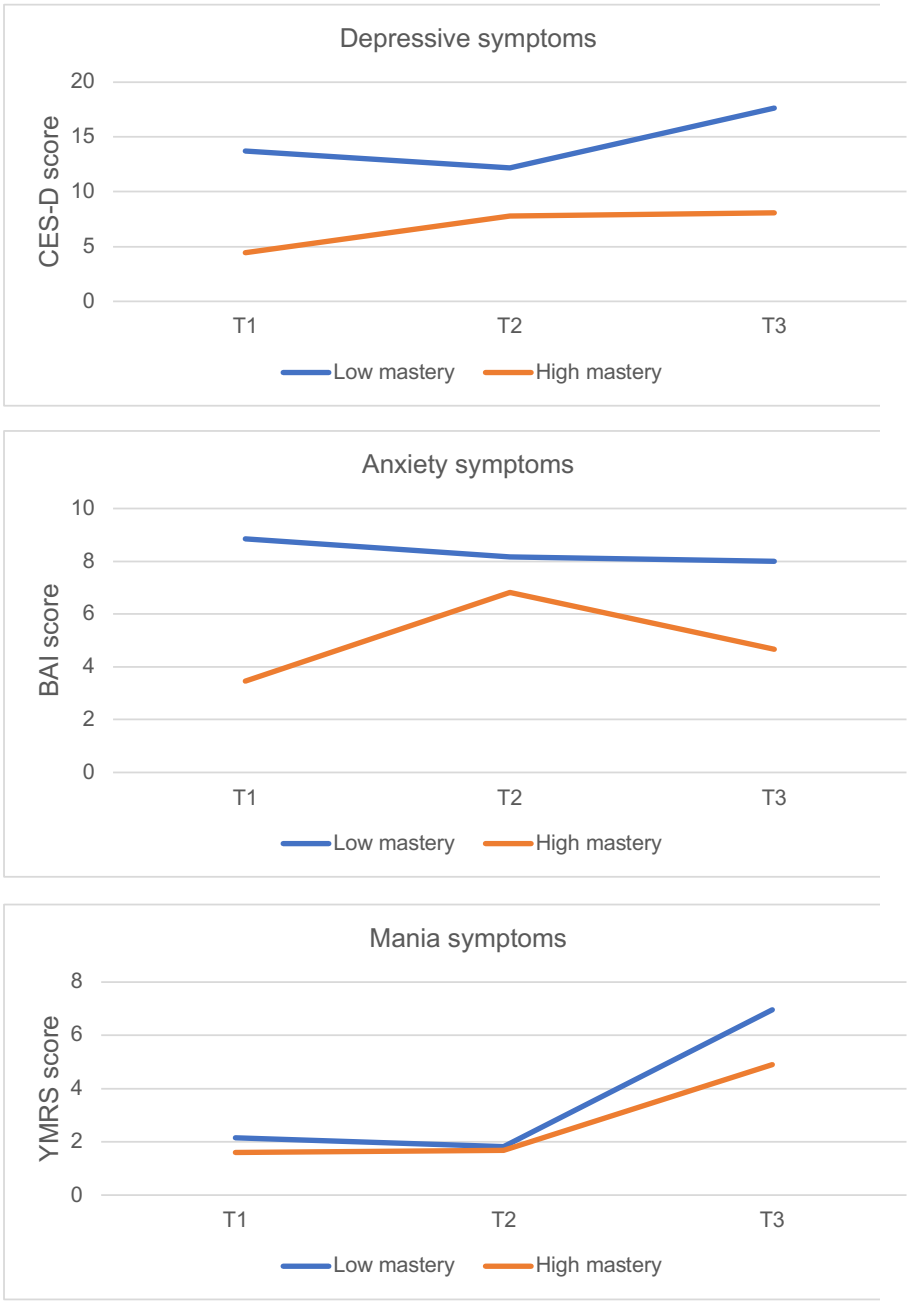


**Figure 3:** Interaction effects between the level of mastery and psychiatric symptoms during T1-T2 and T2-T3

*Note*. T1 = April 2020, T2 = June 2020, T3 = September 2020. Depressive symptoms T1 = T2, T2 = T3, T1 < T3. Anxiety symptoms T1 < T2, T2 = T3, T1 = T3. Mania symptoms T1 = T2, T2 < T3, T1 < T3

## DISCUSSION

This is the first study investigating the course of depressive, manic and anxiety symptoms in OABD during the COVID-19 pandemic. The results of our study show that these symptoms were of relatively low intensity in the first month of the pandemic, but they increased in six months as the pandemic continued. Mastery seemed to be a significant effect modifier of changes for depressive and anxiety symptoms, whereas loneliness did not interact with the course of psychiatric symptoms.

In line with our hypothesis; depressive and mania symptoms increased during the whole period and anxiety symptoms only increased in the first three months of the pandemic, and stayed relatively stable thereafter. In this period, the Netherlands experienced several months of lockdown, with closing of almost all facilities and without a solution in prospect. This increase in symptoms might be an effect of diminishing of the earlier mentioned 'pulling together' effect[12]. Our study is in line with a study conducted in older adults with pre-existing depressive symptoms during COVID-19[22]. In this study, it was observed that during the first two months of the COVID-19 pandemic participants were doing relatively well, but most of the participants forecasted that their mental health would deteriorate as the COVID-19 measures continued. This finding is supported by an often experienced emotionally positive "honeymoon phase" of the disaster response[23]. This concept has been used to describe resilient psychological responses directly following acute disasters, including community bonding and optimism that everything will return to normal quickly. After the "honeymoon phase", the "disillusionment phase" enters. This phase might be represented by the increase in depressive, manic and anxiety symptoms in our group, since this phase includes optimism turning into discouragement and stress concerning the situation increases.

Besides the course of mental health symptoms, we also studied the effect of the sense of mastery on this course. Mastery is seen as a psychological coping resource and has been recognized as an indicator of resilience[14]. In our sample, we found that in the first three months of the pandemic, participants with a higher sense of mastery showed a greater increase in depressive and anxiety symptoms than participants with a lower sense of mastery. However, participants with a higher sense of mastery still showed less psychiatric symptoms, which is in line with an earlier study in younger adult patients that showed that a higher sense of mastery was associated with less depressive symptoms during COVID-19[3].

Additionally, a study on the effects of accumulation of negative life events on depressive symptoms in old age, it was found[25] that the detrimental effect of recent life events on mental health was weaker for persons who had previously been exposed

to more negative events. However, this 'steeling' effect was stronger in persons with *lower* mastery. It is possible that COVID-19 related stressors, including quarantine, fear and loss of loved ones, lead to learning those who felt strongly in control of their lives, that circumstances can actually arise that one cannot control. This might have learned that their more active coping style, fell short in this specific situation. A more passive coping, and thereby having a lower sense of mastery, could be more adequate in this situation. The more passive use of acceptance in combination with novelty seeking as main coping strategies can be useful in chronic circumstances that one has no control over[26]. A high sense of mastery can thus be regarded as non-beneficial when circumstances arise that one cannot control, where it might be more beneficial to accept this and to seek pleasure in other aspects of life. However, in the long run, mastery might contribute to better resilience.

We also found that the initial negative effect of loneliness on mental health symptoms, did not persist after the first three months of the pandemic. In a study conducted in community-dwelling older adults it was found that they experienced an increase in loneliness in the first two months of the pandemic, but mental health remained roughly stable[8]. In our earlier study[3], we have found that loneliness was cross-sectionally associated with depressive symptoms. However, by conducting analyses on interaction effect, we studied whether the increase in symptoms was greater in participants that had high loneliness at t1, when compared to participants that had low loneliness at t1. We did not find any significant interaction effects. However, post-hoc analyses. Revealed that participants that already showed the highest loneliness scores at baseline (highest quartile), also had higher depression scores than the other participants (median = 15 vs. median = 8). Therefore, a greater increase was not to be expected. Thus, loneliness is associated with mental health symptoms[27] but during the pandemic it was not a risk factor for a (further) increase in depressive, manic and anxiety symptoms. This is in line with findings in the general Dutch population, that suggest that the pandemic did not negatively affect the prevalence of anxiety and depression during the first four months, but that loneliness did increase[28]. It was also found in patients with pre-existing psychiatric symptoms, that there was not a strong increase in symptoms during the COVID-19 pandemic in those with a higher burden of disorders. In fact, changes in scores from before to during the pandemic, indicated increased symptom levels in people without psychiatric disorders whereas this was not found in participants with more chronic psychiatric disorders[29].



Our study has several strong points. First, we were able to collect data on different timepoints during this global pandemic. From a scientific perspective, this pandemic offers a unique possibility to study the course of mental health symptoms and risk factors for adverse outcome during a collective negative life event. Despite these

strong points, there are also some limitations that need to be acknowledged. We have included a relatively small group of participants, therefore statements about generalizability should be made with caution. Next, our data were collected in the first six months of the pandemic, thus our findings might not reflect the long-term effects of the COVID-19 pandemic.

The results of our study warrant clinical implications. Clinicians need to be aware of a possible increase of mental health symptoms during a global life event, such as a pandemic and the possible role of inadequate coping strategies as these situations continue. We found that mastery might be beneficial on the short-term, but when uncontrollable events happen, mastery might not be the most beneficial coping style. In addition, it deserves to be stressed that OABD are not experiencing disproportionately increased mental health symptoms, regarding that most participants still do not experience symptoms above the cut-off score. This was also the case for participants that were included at T1, but were lost to follow-up. However, we observed an increase in depressive, manic and anxiety symptoms and therefore this group needs to be carefully monitored as the pandemic continues. In order to prevent further increase of symptoms, clinicians can focus on teaching more adequate coping strategies, e.g., by learning cognitive behavioral therapy (CBT) techniques. CBT aims to improve patients' ability to cope with their illness and possibly their sense of mastery[30]. CBT is a relatively short-term, focused treatment for many types of psychiatric disorders that helps individuals to identify dysfunctional thoughts, attitudes, and behaviors and learn healthier skills and habits[31]. Our study shows a disadvantageous effect of higher mastery for the course of depressive and anxiety symptoms during the COVID-19 pandemic. However, participants with higher sense of mastery still reported less psychiatric symptoms during the COVID-19 pandemic. A suggestion for future research might therefore be looking more closely into the concept of mastery and its effect on mental health symptoms.

## CONCLUSIONS

In conclusion, the COVID-19 pandemic gives us the unique opportunity to study the course of mental health symptoms in OABD whilst experiencing a collective negative life event. OABD were resilient in the first months of COVID-19 outbreak, but mental health symptoms increased as the pandemic continued. Mastery seemed to be a factor that interacted with the course of depressive and anxiety symptoms. This stresses the need to focus on prevention strategies for recurrence in this vulnerable group and to include attention for the sense of mastery as an important part of treatment strategies.

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8

# **PART III:** TREATMENT

# CHAPTER 9

# Evaluating feasibility and satisfaction of a group intervention for mild cognitive impairment in older age bipolar disorder: 'Braintrain'

Sigfried Schouws, Melis Orhan, Nicole Korten, Suzan Zyto, Aartjan Beekman, Ralph Kupka, Erik Scherder & Annemiek Dols

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## KEY MESSAGE

To date, no remediation treatment is available aimed at improving cognitive functioning in patients with older age bipolar disorder (OABD). Our pilot intervention ("Braintrain") included cognitive training, physical exercise and social encounter with peers for OABD and was positively evaluated by the participants. However, its feasibility was limited as few patients fulfilled the inclusion criteria of cognitive and social impairment and retaining the physical ability to walk for a minimum of 30 minutes. OABD patients with cognitive impairment are a vulnerable group for which it is most challenging to design interventions aimed at improving daily functioning.

## INTRODUCTION

Patients with older age bipolar disorder (OABD), defined as bipolar disorder (BD) in people aged over 50 years, often exhibit greater cognitive impairment compared to healthy peers, even between mood episodes[1]. In addition, lower global cognitive functioning has been associated with impairments in social functioning[2]. In the general population of older adults, as well as in patients with mild cognitive impairment or early-stage dementia, interventions aimed at stimulating physical exercise or cognitive training were effective in improving cognitive functioning. Similar positive effects were found in younger patients with BD (recent systematic review[3]), but these strategies are not yet available or tested for efficacy in OABD. Additionally, most cognitive remediation programs for bipolar disorder enroll patients with subjective cognitive complaints. However, objective cognitive impairment is not always accompanied or even preceded by subjective cognitive complaints. Thus, subjective cognitive complaints may not be the best inclusion criterion for cognitive remediation aimed at reducing future cognitive decline. Furthermore, it is difficult for patients to reliably report about their cognitive functioning, and OABD patients have been shown to overestimate their cognitive performances. For this pilot study we used some degree of impaired objective cognitive and social functioning as inclusion criteria and target for treatment.

## INTERVENTION

By combining cognitive remediation with moderately intensive physical exercise and social encounter with peers, we aimed to attract a majority of patients. This pilot study of "'Braintrain'" was conducted with the primary objective to evaluate feasibility and patient satisfaction. The secondary objectives were to measure possible beneficial effects on cognitive functioning, physical strength, social participation, and mood symptoms. After

having attained ethical approval by the institutional review board of the VU University Medical Center, Amsterdam, patients were enrolled from our observational dynamic cohort study (Dutch Older Bipolars: DOBi), in a period of two years (2017-2018). Patients were included according to the following criteria: (1) aged 50 years and over with a DSM-5 bipolar disorder type I or II diagnosis confirmed by MINI-interview; (2) partially remitted or euthymic mood defined as CES-D < 16 (Center for Epidemiologic Studies Depression Scale (CES-D); and YMRS < 12 (Young Mania Rating Scale (YMRS) allowing some degree of subclinical mood symptoms; (3) cognitive impairment of at least -1.0 SD in one or more cognitive domains at neuropsychological examination; and (4) Social and Occupational Functioning Assessment Scale (SOFAS) <60 to ensure some degree of social impairment; (5) self-reported ability to walk at least 30 minutes.

The cognitive remediation program consisted of 12 weekly group sessions each lasting one and a half hour and was based on the functional remediation program from the Barcelona group[4] of which parts had been translated in Dutch and tested to be efficient[5]. The group made a walk in the forest twice a week (one hour and one and a half hour respectively) to stimulate physical exercise in an enriched environment and foster social encounters.

We planned to enroll two groups of 15 patients each with follow-up measurements up to three months after the intervention.

## RESULTS

The intervention was offered three times (fall 2017, $n$ = 6, spring 2018, $n$ = 6, spring 2019, $n$ = 6) and a total of 18 patients were included out of 80 outpatients from the DOBi cohort. Demographic and clinical characteristics at baseline, post-treatment and follow-up are summarized in Table 1. Mean age was 65 ($SD$ = 7.6) and 55% was female.



Five patients could not finish the program due to various reasons (too burdensome $n$ = 2, personal circumstances $n$ = 1, or mood instability $n$ = 2). One patient suffered from a stroke during follow-up, and dropped out.

Participants were not allowed to miss more than three sessions. Most patients succeeded in doing their weekly homework, although for some it was difficult. Homework adherence was influenced by planning skills and motivation. Patients who completed the program ($n$ = 13, 72%), were satisfied with the content of the intervention and evaluated its usefulness as positive. The social aspect of the program was appreciated most. Some participants remarked that they would have appreciated larger groups with a balanced distribution of gender.

**Table 1:** Demographic and clinical characteristics (N=18)

| | Baseline (n = 18) | Post treatment (n = 13) | Follow-up (n = 12) |
|---|---|---|---|
| | **M (SD)** | **M (SD)** | **M (SD)** |
| Demographic variables | | | |
| Age (years) | 65.3 (7.6) | - | - |
| Female (%) | 55 | - | - |
| Education | 5.3 (1.4) | - | - |
| Partner, yes (%) | 68.4 | - | - |
| Clinical variables | | | |
| BD-type II (%) | 58.8 | | |
| Duration of disease, years | 34.5 (17.5) | - | - |
| Age of onset | 32.0 (16.1) | - | - |
| Early onset, yes (%) | 78.9 | - | - |
| Number of admissions | 1.6 (1.2) | - | - |
| Number of episodes | 42.3 (22.7) | - | - |
| Number of somatic diseases | 2.1 (1.5) | | |
| Smoking, yes (%) | 15.8 | - | - |
| Lithiumuse, yes (%) | 64.7 | - | - |
| MMSE | 28.6 (1.7) | - | 28.6 (2.3) |
| YMRS | 1.6 (2.5) | 2.1 (3.4) | 2.1 (2.2) |
| CES-D | 18.0 (8.8) | 14.5 (7.5) | 14.8 (8.4) |
| FAST-O | 20.7 (11.7) | 19.7 (9.8) | 18.1 (8.5) |
| Walking speed | 6.1 (1.1) | 6.4 (1.8) | |
| Grip strength | 25.8 (9.0) | 29.0 (8.5) | |

*Note.* Educational level was assessed by a Dutch scoring system consisting of an 7-point scale, ranging from unfinished primary education (level 1) to university education (level 7). MMSE: Mini Mental State Examnination, YMRS=Young Mania Rating Scale, CES-D=Center for Epidemiologic Studies Depression Scale, FAST-) = Functioning Assesment Short Test for Older adults.

## DISCUSSION

A combination of cognitive remediation, moderate intense physical exercise, and social encounter with peers, as in 'Braintrain', may be a promising treatment option for patients with BD. The program was feasible; most patients completed the program and could follow all the sessions. Drop out was mainly due to personal circumstances. Patients were highly satisfied, especially the social aspect was appreciated.

Inclusion was challenging because patients that fulfill these criteria of cognitive and social impairment often have more physical problems and a less stable mood. As a consequence, a large number of the patients that was eligible for the pilot study did not fulfill the criterion for physical exercise (i.e. be able to walk at least half an hour) and several patients (3 of 18; 17%) had to stop the program because of an increase of mood symptoms.

When using more flexible including criteria for physical exercise, more patients would be able to enroll in such a program. It is assumed that one needs to be at least moderately active for cognitive benefit, but proper adjustments could be made. For instance, the introduction of aerobic exercises instead of walking and the option to follow parts of the exercise program at home at the cost of diminishing the social aspect of the study. Perhaps the most effective way to deliver exercise programs is an individually supervised format preferably in a group setting, although the social aspect of 'Braintrain' was most appreciated. With these adjustments future research can target on a larger group of patients and thus be better able to focus on the effects on cognition and social functioning according to clinical recommendations for trial design by the Targeting Cognition Task Force of the The International Society for Bipolar Disorders (ISBD).



Many cognitive remediation programs enroll patients with subjective cognitive complaints, even though they aim at improving both subjective experience and objective cognitive functioning. 'Brain Train' intended to target objective cognitive impairment. Although participating patients were enthusiastic, many patients could not be included. Our goal to include OABD patients with some degree of cognitive and social impairment was too ambitious as many could not participate in the physical exercise due to comorbid physical problems.

## LEARNING POINTS

- An intervention aimed at improving objective cognitive and social functioning in OABD that includes exercise is difficult as many patients suffer from an additional poor physical condition.
- To ensure personalized care for patients a greater variability and flexibility in physical interventions is needed.

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# CHAPTER 10

# Feasibility and acceptability of group interpersonal and social rhythm therapy (IPSRT) for recurrent mood disorders: A pilot study

Melis Orhan, Nicole Korten, Nina Mans, Anneke van Schaik, Ralph Kupka, Max Stek, Deborah Steenhuis, Moniek van Dijk, Holly Swartz, Patricia van Oppen & Annemieke Dols

*Submitted for publication*

## ABSTRACT

**Background:** Interpersonal and Social Rhythm Therapy (IPSRT) was developed to empower patients with mood disorders by stabilizing underlying disturbances in circadian rhythms in addition to interpersonal psychotherapy strategies. IPSRT has not been studied in a group format for a transdiagnostic sample of patients with major depressive disorder (MDD) and with bipolar disorder (BD). Our primary aim was to investigate feasibility and treatment acceptability of group IPSRT for MDD and BD. Our secondary aim was to investigate the effect of group IPSRT on depressive symptoms and quality of life.

**Methods:** Thirty-six outpatients with either MDD or BD in any mood state, age 36-80 years, were treated with 20 sessions of twice-weekly group IPSRT. Recruitment results, drop-out rates and session adherence were used to assess feasibility. The Client Satisfaction Questionnaire (CSQ-8) and a group feedback session were used to measure treatment acceptability. Pre- to post-intervention changes were measured by the Inventory Depression Symptomatology-Self-Report (IDS-SR) and the Manchester Short Assessment of quality of life (MANSA).

**Results:** Mean age of participants was 65.4 years (*SD* = 10.0). Participants were diagnosed with MDD (n=13; 34.2%) or BD (n=24; 64.9%). Drop-out rate was relatively low (n=9, 23.7%). High CSQ-8 scores (M =26; SD = 4.8) and low drop-out rates indicated feasibility and acceptability of group IPSRT for MDD and BD. Quality of life was significantly higher than baseline ($p$ <.01, Cohen's $d$ = -.44) three months after completion of treatment. No significant differences were found between pre- and post IDS-SR scores.

**Discussion:** It is feasible and acceptable to implement twice-weekly group IPSRT for outpatients with MDD and BD. Future research should evaluate short and long-term efficacy of group IPSRT for MDD and BD of all ages.

# INTRODUCTION

Recurrent mood episodes remain a major challenge for patients with bipolar disorder (BD) and recurrent major depressive disorder (MDD), despite the use of medication[1,2]. Pharmacological treatments are effective in reducing depressive symptoms to some extent, but they have been shown to contribute to somatic comorbidity, illness burden and treatment non-adherence[3] and are often less preferred to psychotherapy by patients with mood symptoms[4]. Treatment strategies with low side effect burden that augment the effects of pharmacotherapy for mood disorders are greatly needed.

Disturbances of circadian biology contribute to recurrent mood episodes in MDD and BD and alterations in the circadian system, including disturbances in the sleep/wake cycle[5,6] are well-documented. Helping patients to develop more regular routines and social patterns may help stabilize circadian abnormalities, thereby reducing mood symptoms[7]. Interpersonal and Social Rhythm Therapy (IPSRT[8]) combines Interpersonal therapy (IPT[9]), based on the principle that relationships and life events impact mood and vice versa, with social rhythm therapy (SRT) elements based on the 'social zeitgeber hypothesis'[10]. SRT states that unstable or disrupted daily routines are linked to circadian rhythm instability and, in vulnerable individuals, to recurrence of mood episodes. Several studies have evaluated the efficacy of individual IPSRT, in BD type I[11], and BD type II[12]. IPSRT is also a promising treatment for MDD: it was found, in a preliminary safety analysis, that IPSRT for MDD had a positive effect on both depressive symptoms and functioning[13].

PSRT group therapy was shown to be feasible in an implementation study conducted in outpatient, inpatient, and intensive outpatient settings[14] with demonstrated improvement of depressive symptoms in the outpatient and intensive outpatient groups. The IPSRT group format was adapted[15] as a treatment option for those who were unable to participate in weekly individual sessions. They tested the group IPSRT intervention in 12 individuals with BD who received open treatment with two individual IPSRT sessions, six IPSRT group sessions, and a 12-week telephone call, showing significant improvements in psychosocial functioning and depressive symptoms at week 12. IPSRT group therapy for BD outpatients was examined in a preliminary efficacy study in a closed, short-term, semi-structured group, with 16 weekly sessions of 2 hours duration[16]. Findings revealed a significant decrease in depressive symptoms and possible reduction in hospital admissions. Group IPSRT has never been formally tested in individuals with MDD or in a combined sample of individuals with both BD and MDD.

The primary aim of this study was to evaluate feasibility and acceptability of group IPSRT when delivered to a transdiagnostic mix of individuals with mood disorders (MDD or BD) aged 18 and over. Our secondary aim was to investigate the effect of group IPSRT on depressive symptoms, quality of life and mastery. We hypothesized that group IPSRT would be feasible and acceptable for patients with both recurrent MDD and BD.

# METHODS

## Patients

Patients were recruited from the outpatient clinics for depression, BD, and old age psychiatry of GGZ inGeest in Amsterdam, the Netherlands. Patients were deemed eligible if they (1) were 18 years or older, (2a) were clinically diagnosed with a recurrent MDD or BD (DSM-5; APA, 2013) or (2b) were in a current depressive episode with the current episode being at least the third episode and lasting shorter than 2 years, and (3) did not meet exclusion criteria. Exclusion criteria were: current psychotic symptoms, severe suicidal ideation, personality disorder as primary diagnosis, current alcohol or substance use disorder and insufficient mastery of the Dutch language for participation in psychotherapy. Concurrent use of all psychotropic medication was permitted. Four groups of IPSRT were conducted ($n = 38$); 34 participants filled out baseline measures, 24 filled out the midpoint measures, 24 filled out the measures after therapy completion, and 27 filled out the measures three months after completion. See Figure 1 for a flow chart.

## Procedure

The study was approved by the Medical-Ethical Committee of the VU University Medical Center (VUmc) in Amsterdam. Participants gave written informed consent prior to enrolling in the study. Participants were invited to two individual IPSRT sessions before starting group sessions in which exclusion criteria were checked; a retrospective life chart of the last 3 years was completed to indicate how many recurrent mood episodes had occurred.

## Measures

Measures were completed at baseline, midpoint, after group IPSRT completion, and three months after completion. After completion of all groups, a feedback session was organized with two participants per group.

### *Demographic and clinical characteristics*

Age and sex of the participants were noted by the therapists at the first individual session.

Clinical diagnosis was obtained from patients' medical records and checked by a retrospective life chart and Mood Disorder Questionnaire (MDQ[17]), using DSM 5 criteria[18]. Current depressive symptoms were measured with the 28-item Inventory Depression Symptomatology- Self-Report (IDS-SR[19]).

***Mania symptoms.***

Current mania symptoms were measured with the Young Mania Rating Scale (YMRS[20]). Quality of life was measured with the Manchester Short Assessment of quality of life (MANSA[21]). To assess whether patients experienced more control over their mood symptoms and interpersonal problems, the Pearlin Mastery scale[22] was used.

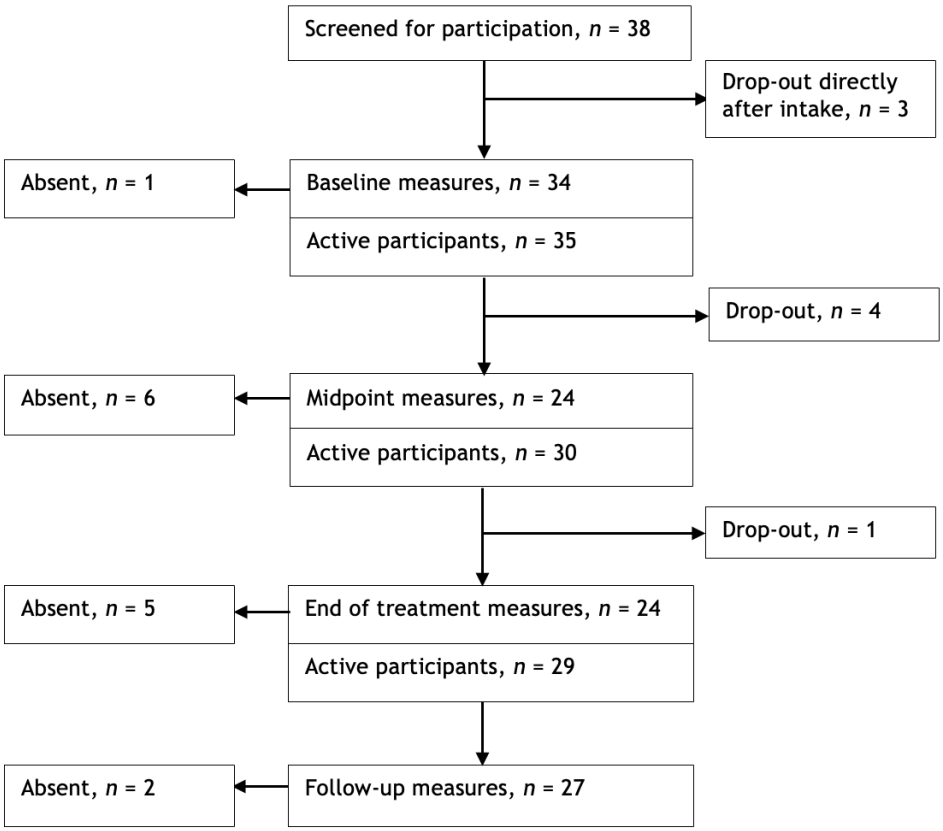


**Figure 1:** Flow chart of inclusion for the intervention

***Feasibility and treatment acceptability***

Feasibility was measured by recruitment results, drop-out rates and session attendance. Drop-out was defined as not completing all group therapy sessions and missing the post treatment measure. Treatment acceptability was assessed via the client satisfaction questionnaire (CSQ-8[23]) after completion of the group-IPSRT and an open feedback session. The CSQ is an 8-item questionnaire with answers on a 4-point scale, with scores ranging from 8 to 32. Higher scores indicate higher satisfaction levels. We added three additional questions to the CSQ-8; '*Was the group size sufficient for you?*', '*Did you experience it as a problem that persons in the group were not diagnosed with the same disorder*?', '*Did you experience it as a problem that persons in the group were of different ages than you*?', also answered on a 4-point scale '*certainly not, I don't think so, I think so, certainly*'. During the open feedback session with 8 participants (2 participants from each IPSRT group), two researchers conducted feedback via 5 questions (1) '*What did you, in general, appreciate about the IPSRT group treatment',* (2) '*More specifically, what did you appreciate about the IPSRT group treatment?', (3) 'What do you think was missing or omitted from the group IPSRT treatment?'*, (4) '*What is your opinion about having a group that included individuals with different diagnoses (MDD/BD),* (5) '*What are things that could be done differently?*'.

## IPSRT group treatment

The IPSRT group treatment was adapted from 'A manual for the adaptation of individual interpersonal and social rhythm therapy (IPSRT) to group outpatient treatment for bipolar disorder'[14]. IPSRT is implemented in a series of four phases[24], starting with a history-taking and assessment of the nature and quality of patients current and past interpersonal relationships. Thereafter, patients are helped to establish more regular daily social routines. Subsequently, capability is increased to use the skills learned in the acute phase of treatment to maintain current euthymic mood, level of functioning, and social rhythm regularity. The final phase of treatment focuses on impending termination. The Social Rhythm Metric[25] (SRM) is introduced in the initial phase, and patients fill out SRMs daily during the treatment period. In this study, the SRM was used clinically to aid participants in increasing the regularity of their daily routines but was not scored for research purposes.

Each group had a maximum of 12 participants and was led by two therapists (a psychologist and mental health nurse). IPSRT consisted of 20 twice-weekly, two-hour sessions, delivered over 10 weeks. A frequency of two sessions per week was chosen based on results of a recent RCT[26], showing that twice weekly sessions of cognitive behavioral therapy and IPT lead to faster and better depression outcomes than weekly sessions.

### Statistical analyses

Characteristics of the study sample at baseline were summarized with descriptive statistics. Recruitment was assessed by the percentage of participants recruited by each outpatient clinic, drop-out rates were assessed by the percentage of participants that dropped out and the average number of adhered sessions was used to indicate session adherence. Satisfaction was indicated by the average CSQ scores and more qualitatively by results of the open feedback session. To evaluate changes in depressive symptoms, quality of life, and sense of mastery were compared pre- and post- intervention using paired sample t-tests. Enduring effects of the intervention were analyzed by conducting paired sample t-tests comparing the same variables pre-intervention to follow-up three months post-interventions. Effect sizes were computed using Cohen's *d*. Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 25.0, SPSS Inc., Chicago, IL).

## RESULTS

### Sample

Our study sample consisted of 38 participants, including 27 (71.1%) women. Participants had a mean age of 65.4 years (*SD* = 10.0). Table 1 describes the demographic and clinical characteristics of our intent-to-treat study sample. 64.9% (*n* = 24) was diagnosed with BD and 34.2% (*n* = 13) with MDD. Our sample had a mean IDS-SR score of 11.1 (*SD* = 8.0) at baseline, indicating a low level of depression severity on average. Our sample had a mean YMRS score of 4.4 (*SD* = 5.1) at baseline, indicating remission of mania symptoms.

### Feasibility

#### *Recruitment*

Participants were a convenience sample recruited from the outpatient clinics for depression, BD, and old age psychiatry in order to obtain a transdiagnostic mix of individuals with mood disorders of all ages. However, the IPSRT therapists mostly worked at the old age psychiatry outpatient clinic. It was therefore more difficult to recruit patients from the other outpatient clinics. The vast majority (92.1%, *n* = 35) of participants was recruited from the old age outpatient clinic; at the time of inclusion, 63.2% of participants (*n* = 24) were aged 65 years and over.

**Table 1:** Demographic and clinical characteristics of the study sample at inclusion (*n* = 38)

| Variable | |
|---|---|
| **Demographic variables** | |
| Gender, woman, % (n) | 71.1 (27) |
| Age, M (SD), range | 65.4 (10.0), 26 – 79 |
| **Clinical variables** | |
| Diagnosis | |
| Bipolar disorder, % (n) | 64.9 (24) |
| Major depressive disorder, % (n) | 34.2 (13) |
| IDS-SR score, M (SD), range | 11.1 (8.0), 0 - 26 |
| YMRS score, M (SD), range | 4.4 (5.1), 0 - 22 |
| MANSA, M (SD), range | 53.4 (10.3), 31 - 72 |
| Mastery, M (SD), range | 21.6 (4.4), 9 - 30 |

*Note.* M = mean, SD = standard deviation, IDS-SR = Inventory Depression Symptomatology-Self-Report, YMRS = Young Mania Rating Scale, MANSA = Manchester Short Assessment of quality of life.

### *Drop-out rates and adherence*

Of the intent-to-treat sample, 9 participants (23.7%) dropped out of the IPSRT group after inclusion due to: withdrawal before the first treatment session (*n* =3), finding the group too confrontational (*n* = 2), increase of symptoms (*n* = 2) and unknown reasons (*n* = 2). The mean number of sessions attended was 16.3 (*SD* = 2.9), with a range from 10 to 20 sessions.

## Acceptability

The mean CSQ-8 score post-treatment for those who completed the intervention, was 26 (*SD* = 4.8, range 15-32), indicating a high level of satisfaction. The quality of the intervention was rated as good by 63.0% (*n* = 17) and as excellent by 22.2% (*n* = 6). 55.6% (*n* = 15) of the participants reported being very satisfied with the amount of help they received. 81.5% (*n* = 22) reported that the intervention helped them cope with their problems. 85.2% (*n* = 23) was satisfied with the size of the group, 85.2% (*n* = 23) was satisfied with the mix of diagnoses of the group members and 92.6% (*n* = 25) was content with the large variety of ages.

### *Feedback from participants*

During the open feedback session, participants remarked that they were pleased with the group format, noticing that the twice weekly sessions offered them structure (*"It was tough, but it brought me a certain continuity"*. "*The frequency of the group gave me structure and a goal: having to be somewhere at a specific time, two times a week, and filling out the SRM"*). Participants noticed a difference between participants with and without a history of manic episodes ("*Apathy is my biggest enemy. It made me sad that*

*people kept describing their manic episodes"*), but that this was mostly due to a difference in experiences. It was remarked that the level of input during the sessions strongly differed between participants.

## Clinical symptoms

### *Mood symptoms*

Table 2 summarizes average mood symptoms and the results of the paired sample t-tests on each timepoint. Mean IDS-SR was 11.1 (*SD* = 8.0) pre-treatment, 11.8 (*SD* = 7.1) post-treatment, and 7.6 (*SD* = 7.3) at three-month follow-up. These symptoms were not statistically different between pre- and post-intervention and pre-intervention and 3-month follow-up (resp. $t(21) = .33$, $p = .74$, $d = .07$ and $t(25) = 1.98$, $p = .06$, $d = .39$).

### *Quality of life*

Mean MANSA score was 53.4 before treatment (*SD* = 10.3), 56.1 (*SD* = 12.2) post-treatment and 56.4 (*SD* = 11.6) at three-month follow-up. These scores were not statistically different from pre- to post treatment ($t(19) = -1.98$, $p = .06$, $d = -.44$), but there was a significant increase from pre-treatment to 3-month follow-up ($t(18) = -2.99$, $p < .01$, $d = -.69$).

### *Mastery*

Mean mastery score was 21.6 (*SD* = 4.4) pre-treatment, 22.6 (*SD* = 6.3) post- treatment, and 22.4 (*SD* = 5.1) at three-month follow-up. These scores were not statistically different between these timepoints (resp. $t(25) = -1.02$, $p = .32$, $d = -.20$ and $t(26) = -.76$, $p = .45$, $d = -.15$).

**Table 2 :** Average mood symptoms and results of paired sample t-tests between pre intervention and post intervention, and between pre intervention and follow-up

| | Pre intervention (*n* = 34) | | During intervention (*n* = 24) | | Post intervention (*n* = 24) | | Follow-up (*n* = 28) | | p-value pre-post | Cohen's d | p-value pre-follow-up | Cohen's d |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | SD | M | SD | M | SD | M | SD | | | | |
| IDS-SR | 11.1 | 8.0 | 11.3 | 9.9 | 11.8 | 7.1 | 7.6 | 7.3 | .74 | .07 | .06 | .39 |
| YMRS | 4.4 | 5.1 | 4.8 | 5.3 | 4.5 | 5.7 | 3.2 | 5.2 | .50 | -.15 | .24 | .26 |
| MANSA | 53.4 | 10.3 | 54.0 | 11.5 | 56.1 | 12.2 | 56.4 | 11.6 | .06 | -.44 | <.01** | -.69 |
| Mastery | 21.6 | 4.4 | 23.1 | 5.8 | 22.6 | 6.3 | 22.4 | 5.1 | .32 | -.20 | .45 | -.15 |

*Note.* M = mean, SD = standard deviation, IDS-SR = Inventory Depression Symptomatology-Self-Report, YMRS = Young Mania Rating Scale, MANSA = Manchester Short Assessment of quality of life. * = p <.05, ** = p <.01

## DISCUSSION

Our results show that group IPSRT for participants with BD and MDD is feasible and acceptable in an outpatient setting. It was difficult to recruit a mix of ages because of staff allegiance to specific clinics, but feasible to recruit a mix of diagnoses. The group intervention was well-received by participants and resulted in high treatment adherence and satisfaction. Quality of life was significantly higher three months after completion of the treatment when compared to baseline, but no changes were observed in depressive symptoms or mastery scores.

The primary aim of our study was to investigate the feasibility and acceptability of group IPSRT in an outpatient setting with both MDD and BD patients. In line with our hypothesis, we found high treatment adherence (< 25% drop-out rate), indicating feasibility. Satisfaction among participants was high based on CSQ-8 scores, indicating acceptability. Subjectively, participants did not experience problems with the differences in diagnosis MDD or BD and the twice weekly sessions. To our knowledge, this is the first pilot study in which IPSRT was given twice a week to a group of outpatients with MDD or BD. One other study[13] also included MDD patients together with BD patients in an IPSRT group treatment with one weekly session, and found no adverse effects. Otherwise, IPSRT has only be previously evaluated in those with BD[14,15,16,27]. Our study strengthens the literature showing that group IPSRT is feasible and acceptable for BD patients and extends these findings to show that it is also feasible and acceptable for mixed groups of BD and MDD patients. Demonstrating feasibility and acceptability of this approach may be important for dissemination of IPSRT groups in routine practice settings where it is often necessary to provide services to individuals with heterogenous needs and clinical presentations.

It proved challenging to recruit participants from outpatient clinics other than those where the therapists were working. Therefore, our sample consisted primarily of older (≥ age 60) adults, adding to the limited evidence of feasibility and acceptability of this approach in late life. Further studies should examine the acceptability and feasibility of group IPSRT for a wide range of ages.



The secondary aim of our study was to investigate the effect of group IPSRT on depressive symptoms. Our results show that depressive symptoms did not change immediately after the treatment, but decreased slightly at three months after completion. This is not in line with previous pilot studies showing a reduction in depressive symptoms following group IPSRT[14,15,16,13,27]. However, at the start of treatment, our group had relatively low depression scores which might have caused a "floor effect." Our decision to include individuals with a lifetime history of MDD or BD but not necessarily currently

being in a depressive episode may have also limited our ability to detect changes in depressive symptoms. Due to this inclusion criterion, we were able to include more participants, but participants already had such low depression scores that improvement was not to be expected.

Quality of life slightly improved pre- to post- treatment and was significantly higher three months after completion of the treatment, when compared to baseline. Although participants were positive about the twice weekly sessions, participants noted that a lot of information was covered in 10 weeks, suggesting that participants may have needed additional time to process and apply the learned techniques in their daily life. This may explain on-going improvements in QOL, even after the intervention was over. Since the current study was an uncontrolled pilot study with the focus on feasibility, effects on outcomes should be considered preliminary. Nevertheless, our findings might indicate a delayed effect of group IPSRT on quality of life.

Our study has several strengths. This was the first study to investigate the feasibility and acceptability of group-IPSRT for patients with either MDD or BD diagnoses. Also, we were able to assess feasibility with both quantitative and qualitative data to better assess acceptability. There were, however, several limitations. Because the sample size was small and no control group was included, we are unable to make definitive statements about the impact of the intervention on symptoms and functioning. To draw more robust conclusions about the efficacy of IPSRT for treating depressive symptoms, controlled studies with larger sample sizes are needed. In addition, our study did not take in to account whether participants used medications during and after the treatment which may have confounded study findings. Finally, our sample had relatively low depression severity scores at baseline, which might have led to a bias in our results. When included participants are already in remission, longer follow-up periods are necessary in order to draw conclusions about the impact of the intervention on risk for recurrence of mood symptoms. This study was not designed to evaluate recurrent risk.

Multiple studies have shown that group IPSRT is feasible in different treatment groups; inpatient, outpatient, combination of MDD and BD and in both younger and older adults[14,16,15,13,27]. Future studies should examine the efficacy and effectiveness of group IPSRT on depressive symptoms in terms of response and remission for both MDD and BD patients. Our study findings should inform future study designs, such as demonstrating that twice-weekly sessions are both feasible and acceptable and that patients with both MDD and BD can be treated in the same groups. It will also be important to assess participants at least 3 months post treatment given our finding of continued impact on QOL over this time frame.

In conclusion, this pilot study shows that it is feasible and acceptable to implement a group IPSRT intervention with twice-weekly sessions for a mixed group of outpatients with MDD or BD diagnoses. Future research should evaluate the effect of this treatment on long term outcomes and rates of recurrence.

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# CHAPTER 11

# General discussion

The first aim of this thesis was to expand our knowledge on the diagnostics and assessment methods in OABD. With this aim, we first examined whether different depression scales can be harmonized in order to create larger datasets. Then, we examined the reliability and validity of the Functioning Assessment Short Test (FAST) for Older adults (FAST-O). Next, we compared cognitive functioning in OABD with cognitive functioning in late life depression and healthy controls. The second aim of our thesis was to create a greater understanding of the clinical phenotype in OABD and its mutual interactions. For this aim, we first examined the relationship between cognitive and social functioning in OABD. Thereafter, we studied the influence of social, psychological and cognitive factors on the clinical course in OABD. Next, we studied psychiatric symptoms during the COVID-19 outbreak in OABD and at last, we studied the course of these psychiatric symptoms in OABD during the first 6 months of the COVID-19 pandemic. Our third aim was to assess the feasibility and acceptability of new treatment approaches in OABD. We first examined a group intervention for mild cognitive impairment in OABD and thereafter we studied an intervention of group interpersonal and social rhythm therapy (IPSRT) for recurrent mood disorders.

## SUMMARY OF MAIN FINDINGS

***Diagnostics***

In **chapter 2**, we compared associations between categorical and continuous and harmonized measures of depression and global functioning in a large dataset of OABD in order to examine whether different depression severity scores can be harmonized in a large dataset. In the Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD[1]) the 17-item Hamilton Depression scale (HAM-D[2]), Montgomery Asberg Depression Rating Scale (MADRS[3]) or the Center for Epidemiological Studies Depression scales (CES-D[4]) was used to assess current depressive symptoms, while the Global Assessment of Functioning (GAF[5]) assessed functional status. Data were harmonized from 8 OABD studies ($n$ = 582). Effect size and variance explained by the model for the categorical measure in the total sample was higher than both the categorical and continuous measure in the CES-D subsample, higher than the categorical but lower than the continuous measure in the HAM-D subsample, and lower than both the categorical and continuous measures in the MADRS subsample. It was found that associations were only slightly larger for the continuous vs. categorical measures of depression scales. Therefore, we can conclude that harmonizing different depression scales into ordinal categories for analyses is feasible without losing significant statistical power.

In **chapter 3**, we validated an adapted version of the Functioning Assessment Short Test (FAST[6]), for OABD (FAST-O). The original FAST was developed in order to tackle the

problem that many frequently used instruments fail to assess psychosocial functioning in patients with BD. However, the original FAST is not fully applicable in older adults, due to the domain of occupational functioning. We adapted the items in the area of "work-related functioning" of the FAST into items assessing "societal functioning". We found that the internal structure of the FAST-O, measured by confirmatory factor analysis, was mostly similar to the internal structure of the original FAST. The internal consistency was excellent. The concurrent validity when correlated with the Social and Occupational Functioning Assessment Scale (SOFAS[7]) was low, but significant. The FAST-O was able to distinguish between euthymic and symptomatic OABD patients. Therefore, we concluded that the FAST-O has strong psychometric qualities and based on our results, we concluded that the FAST-O is a short, efficient solution in order to replace global rating scales or extensive test batteries in order to assess daily functioning of older psychiatric patients in a valid and reliable manner.

In **chapter 4**, we compared cognitive functioning in OABD to cognitive functioning in late life depression (LLD) and healthy controls (HC). We compared OABD, LLD and HC in their cognitive functioning on different neuropsychological tests. We divided cognitive functioning into four different domains: episodic memory, processing speed, interference inhibition and working memory. Our findings showed that OABD and LLD patients exhibit more cognitive dysfunction then HC, with OABD showing worst cognitive functioning on all cognitive domains, except for interference inhibition. These differences remained significant, even after controlling for the effect of depressive symptoms at the time of testing. These findings suggest that cognitive dysfunction in OABD is more severe in magnitude, albeit in the same domains as LLD. This difference can thus not be fully explained by the severity of depressive symptoms.

***Understanding***

In **chapter 5,** we studied the relationship between cognitive and social functioning in OABD. We included different domains of cognitive functioning and studied the association with different aspects of social functioning. We found that global social functioning, number of meaningful contacts and social participation were not interrelated. In addition, we found that global cognitive functioning, learning and memory and executive functioning were positively associated with global social functioning. No associations were found between cognitive functioning and social participation or meaningful contacts. Depression severity and disease duration were no effect modifiers. Global social functioning judged by the clinician was found to be independent of social functioning defined by the number of social contacts and social participation as reported by the patient. Global social functioning was positively related to cognitive functioning.

In **chapter 6** we focused on social, psychological and cognitive factors that might be associated with recurrence in OABD in a longitudinal study design. Social factors that we included were partner status, children status, global social functioning and social support. The psychological factors that we included was coping styles, and cognitive factors were cognitive functioning in the domains of attention, learning/memory, executive functioning and verbal fluency. We did not find any significant associations between the social, psychological and cognitive factors and having a recurrence during the three-year follow-up period. However, participants in the recurrent group were younger, more often female and less likely to have children. Our results suggest that results from the adult bipolar disorder population cannot be extrapolated to OABD patients.

In **chapter 7** we included a sample of OABD patients in order to study factors that were associated with psychiatric symptoms during the first month of the COVID-19 pandemic. During the first month of the COVID-19 pandemic, particularly older adults were advised to stay at home as much as possible and to limit social contacts. This provided us the unique opportunity to study factors related to recurrence of mood symptoms, during a collective life event. We compared factors that were measured three years before the COVID-19 outbreak with factors during the COVID-19 outbreak. We found that participants experienced less psychiatric symptoms during COVID-19 when compared to their baseline measurements, three years before. There was no difference in loneliness between COVID-19 and baseline. Cross-sectionally, we found that having children, more feelings of loneliness, lower mastery, passive coping style and neuroticism were associated with more psychiatric symptoms during COVID-19 measures.

In **chapter 8** we studied the course of psychiatric symptoms in OABD during the first six months of the COVID-19 outbreak and its association with loneliness and mastery. We found that depressive, manic, and anxiety symptoms increased during the first six months of the pandemic. Mastery seemed to be a factor that interacted with the course of depressive and anxiety symptoms. Participants with higher levels of mastery experienced a greater increase of symptoms, but still experienced less symptoms than participants with lower levels of mastery. Loneliness did not interact with the course of the psychiatric symptoms. We have found that OABD patients were resilient in the first months of COVID-19 outbreak, however, depressive, manic and anxiety symptoms increased as the pandemic continued.

***Treatment***

In **chapter 9** we studied the feasibility and satisfaction of a group intervention for mild cognitive impairment in OABD, called "Braintrain". The treatment program consisted of a

combination of cognitive training and physical activity, and has been studied before in younger adult BD patients. Inclusion was possible when participants showed objective cognitive dysfunction and were able to walk for 30 minutes. The primary objective of "Braintrain" was to evaluate the feasibility and patient satisfaction of this treatment program in OABD. The secondary objectives were to measure possible beneficial effects on cognitive functioning, physical strength, social participation and mood symptoms. The intervention was offered to three groups of OABD, and a total of 18 participants were included. Participants were not allowed to miss more than three sessions and most patients succeeded in doing their weekly homework, although for some it was difficult. The social aspect of the program was appreciated most by the participants. It was difficult to include participants based on their objective cognitive functioning state because it was seen that many patients suffer from an additional poor physical condition. To ensure personalized care for patients, a greater variability and flexibility in physical interventions are needed.

In **chapter 10**, we investigated the feasibility and acceptability of group Interpersonal and Social Rhythm Therapy (IPSRT[8]). Thirty-six outpatients with either a diagnosis of BD or major depressive disorder were included. IPSRT was developed to empower patients with mood disorders by stabilizing underlying disturbances in circadian rhythms in addition to interpersonal psychotherapy strategies. It had not been studied in a group format including both patients with major depressive disorder and BD. We found that it was feasible and acceptable to implement twice-weekly group IPSRT for this group. In addition, quality of life improved three months after completion of treatment.

## INTEGRATION OF THE MAIN FINDINGS

***Diagnostics***

The classification of BD is mostly based on its clinical appearance, whereas the first chapters of this thesis show that the classification of BD is more comprehensive than just the presence of affective episodes. With treatment being mostly targeted at the remission of mood symptoms, the inclusion of functioning aspects is often neglected. It was found (**chapter 3**) that the presence of current depressive symptoms is strongly related to daily functioning, despite the use of different depression severity scales. However, functional recovery is not always present, even after remission of mood symptoms. Functioning in BD is a multifactorial construct[9,10,11], with OABD exhibiting dysfunction in multiple areas, among which cognitive functioning (**chapter 4**). Cognitive functioning is important for our daily functioning, where it is needed to plan activities, remember things, focus attention and shift between different tasks[12]. It was found that OABD showed worse cognitive functioning in all cognitive domains when

compared to late life depression (LLD) patients and healthy controls (HC). In addition, differences in cognitive functioning between these groups could not be fully explained by current depressive symptoms (**chapter 4**), and thus are likely to still be present when mood symptoms are in remission. It is estimated that about 40% of OABD patients present cognitive dysfunction[13,14] and that cognitive functioning may be worsened by the course of BD[15,16], with additional consequences for daily functioning. In OABD, functioning may become even further limited as a result of various factors, such as a decrease in social network size and reduced mobility[17]. More and more, researchers and clinicians are not only focused on clinical remission, but attention for functional recovery and well-being is more prioritized[18]. However, making a reliable estimation of the current level of functioning in OABD can be difficult. Currently often used instruments to assess daily functioning, such as the Global Assessment of Functioning Scale (GAF[5]) are not fully applicable for the older patient population, since significant parts of these functioning scales often refer to patients' occupational functioning. To assess the current level of functioning, we have successfully adapted the Functioning Assessment Short Test (FAST[6]) to a version that can be used to assess daily functioning in OABD (FAST-O; **chapter 3**). In order to do so, the section "occupational functioning" was replaced by "societal functioning" to increase the applicability in the older patient population. By studying the reliability and validity of the FAST-O, we have found that the FAST-O is a short, efficient solution in order to replace global rating scales or extensive test batteries in OABD (**chapter 3**). The findings in **chapter 2, 3 and 4** show that OABD exhibit dysfunction in various domains and that with appropriate adjustments, already existing instruments can be used to make an estimation of the current level of functioning of the individual. These findings emphasize the importance of including multiple functioning domains in clinical practice for this specific group.

***Understanding***

The clinical phenotype of OABD knows great variability and mutually related factors that underline the complexity of the disorder. It was found that OABD exhibit more cognitive dysfunction than LLD and HC (**chapter 4**), where we have also found that cognitive dysfunction is related to other aspects of functioning, for instance to social functioning (**chapter 5**). We found that different measures of qualitative and quantitative social functioning were not interrelated, where only a qualitative measure of social functioning was found to be associated with cognitive functioning (**chapter 5**). This indicates that merely the quality of social interactions seems to be affected by cognitive dysfunction and not just the quantity of social relationships. Up until now, most studies in OABD have been studying these factors cross-sectionally and it still remains unknown what factors are related to recurrence in this group. Earlier it was found in the DOBi-cohort, that no associations were found between recurrence in OABD and several clinical predictors, such as physical illness, age at onset, onset polarity,

and predominant polarity[19]. In younger adults, findings indicate that poor social functioning[20], not having a partner[21], more emotion oriented and avoidance coping strategies[22], and worse cognitive functioning[23] have all been associated with a shorter time to relapse and more depressive episodes. On that note, we have broadened our scope and we investigated the association between several social, psychological and cognitive factors and recurrence at three-year follow-up (**chapter 6**). We did not find any significant associations, but we did find that 37.5% of all participants experienced one or more recurrences, and that participants in the recurrent group were younger, more often female, and had less often had children. In the beginning of 2020, the COVID-19 pandemic started and several measures were set-up in order to reduce the spread of the virus. During the first six months of the pandemic, we were able to continue study recurrence in the DOBi cohort during the experience of a collective life event (**chapter 7**), and thus being exposed to more or less the same circumstances. Our participants experienced a decrease in mood symptoms during the first month of the pandemic, when compared to symptoms three years before the pandemic. This was different when compared to findings in the younger adult BD population[24], where it was observed that there was an increase in manic symptomatology. Older age thus seemed to be a protective factor, where other studies showed that adolescents and young adults have been disproportionately negatively affected when compared to younger children and older adults, and it is hypothesized that this might be the result of different unfavorable behavioral and social changes[25]. However, there was a subgroup in our sample that did experience a recurrence of mood symptoms during COVID-19, and cross-sectionally we found that recurrence of mood symptoms was associated with not having children, more feelings of loneliness, lower mastery, a more passive coping style and higher neuroticism. When looking longitudinally into the course of mood symptoms during COVID-19, we found that mood symptoms increased over time (**chapter 8**). Mastery played an important role in the course of these mood symptoms, with participants with higher mastery showed a greater increase in mood symptoms in the first three months. However, despite a greater increase of symptoms, participants with a higher sense of mastery still experienced lower levels of mood symptoms than participants with a lower sense of mastery. This indicates that mastery might play an important role in the of resilience in this group. Although OABD is often regarded as being capricious, our group experienced less mood symptoms during the COVID-19 pandemic when compared to three years before (**chapter 7**) and also in our earlier study (**chapter 6**) we found that at three-year follow-up, 60.9% of our participants were non-recurrent, and of all participants 28.1% had one recurrence.



***Treatment***

Over the last years, attention has risen for the development and implementation of psychological treatments for BD[26], for instance cognitive and family-focused therapies.

However, most of these treatments are often designed for the younger adult BD patient group and therefore these interventions might not always be suitable for OABD. In the first part of this thesis, it is shown that even after symptom remission, dysfunction in other areas is present (**chapter 2**), for instance in the areas of daily functioning (**chapter 3**), social functioning (**chapter 5)** and cognitive functioning (**chapter 4**). So besides focusing on clinical remission, for instance by using medication, other aspects of OABD also need to be incorporated in order to achieve functional remission as well. Since OABD patients exhibit significant cognitive dysfunction (**chapter 4**), a first important focus for treatment would be to improve cognitive functioning. An already existing program was adapted for the older patient population and we have found that redesigning a study protocol specifically for OABD patients also knows its difficulties (**chapter 9**). For instance, inclusion criteria need to be reconsidered and cannot be extrapolated from research in the younger patient group. We found that inclusion for this treatment program, consisting of cognitive remediation and physical activity for participants with objective cognitive impairment, was difficult. Most participants that met the inclusion criterium of objective cognitive impairment did not meet the criterium of having the ability to walk for at least 30 minutes (**chapter 9**). However, inclusion does not always have to be difficult in the older patient population. In our second pilot study (**chapter 10**), our aim was to include participants with a variety of ages, where we mostly included participants aged 60 and over. In this study, we applied group IP-SRT to a group of participants with either BD or unipolar depression. This intervention was feasible and it was acceptable to have two sessions per week, where this was only given once per week in previous studies. This psychological treatment resulted in high satisfaction amongst participants, low drop-out rates and an improvement in quality of life (**chapter 10**). Findings from these studies (**chapter 9 & chapter 10**) indicate that already existing study protocols cannot be plainly used in the older patient population, but that careful reconsideration of the content and in- and exclusion criteria is necessary. Specific attention needs to be given to population-specific criteria, for instance current physical condition and cognitive functioning.

# METHODOLOGICAL CONSIDERATIONS

## Strengths and limitations

Besides the strengths and limitations mentioned in each individual research paper, there are some general strengths and limitations that need to be acknowledged.

### *Cohort studies*

Results in this thesis were mostly based on cohort studies: DOBi[27], NESDO[28] and studies included in the GAGE-BD consortium[1]. Due to the relatively great sample sizes, we were able to collect a wide range of data. This gave us the opportunity to study the

interaction of several factors in OABD and to compare these with data in other groups all over the world. However, cohort studies also have some limitations. In most of our studies, variables were measured cross-sectionally. Therefore, no definitive conclusions could be made considering the causality of our findings. Also, among cohort studies, both fixed and fixed prospective study designs are used. The DOBi study is a fixed study design. A major disadvantage of dynamic prospective studies is that the sample size might decline, due to a loss to follow-up. This is especially the case in older patient populations.

***Selected population***

Most of the included studies are conducted in the Netherlands, whereas in **chapter 2** also participants were included from other parts of the world. However, our conclusions mostly relate to WEIRD people (white, educated, industrialized, rich, and democratic[29]). Also, we mostly included participants that were in touch with specialized mental health care services at the time of testing. There might be patients with BD that do not receive frequent specialized care, or are only seen by their general practitioners. Therefore, our group might represent the patient group that is more severely ill. This is also referred to as Slater's fallacy, which in this context means that patients who have multiple episodes are probably overrepresented in a cross-sectional sample[30,31]. On the other hand, we have focused on the older patient population in our studies. Interpretation of our findings must therefore take into account the possibility that a "healthy survivor" effect might play a part in these findings. This means that individuals who die prematurely or who are too ill to participate in research studies, could bias sample characteristics to favor older adults who are doing relatively well. All these points illustrate that we studied a selected population, and therefore conclusions should be taken with caution.

***Normal aging versus pathological aging***

In most of the studies in this thesis, we studied several characteristics within populations, particularly within the OABD population. However, even in normal aging, people experience enormous changes in their lives, for instance in their cognitive and daily functioning. Since we have focused merely on psychiatric patient populations, it remains unclear whether our findings only reflect characteristics of the OABD population, or if and to what extent they also occur in older individuals without BD. Thus, it remains unclear whether our found associations are a part of normal aging or if they indicate pathological aging. In order to draw conclusions about the clinical relevance of our findings, it is therefore necessary to include control groups in future research.

## CLINICAL IMPLICATIONS

The Dutch population is aging rapidly, and specific recommendations for diagnosing and treating OABD are warranted. Based on findings in this thesis, multiple clinical implications can be distilled.

1. OABD are a distinct group and results from younger adult patients cannot be extrapolated to this group

In current research, relatively little attention has been given to the older patient population when compared to the younger adult patient population. Most research, diagnostic methods and treatment strategies are developed for younger adult patients and are similarly used for older patients. However, in this thesis it was found that findings in OABD differ from findings in the younger adult BD population. Our findings show that factors that were associated with recurrence in the younger adult BD group, were not associated with recurrence in OABD (**chapter 6**). Also, the results obtained during the COVID-19 pandemic differed between younger and older adult BD patients (**chapters 7 & 8**). This underlines that OABD are a distinct group, and that results from younger adult patients cannot be extrapolated to this group. Clinicians need to be aware of the distinction between these groups and the additional different areas of focus during the diagnostic and treatment phase.

Most assessment and measurement methods are developed for younger adult patients, in which items are used that might not be fully applicable to older adults. This results in a lack of essential information, for instance concerning the current state of functioning. Our findings implicate that instruments need to be evaluated by their usability, and that adaptations need to be made where possible. This is also the case for the implementation of treatment strategies that are proven to be effective in the younger adult population. Clinicians need to be aware of the specific characteristics of the OABD group, such as somatic comorbidities and cognitive dysfunction, and what impact these characteristics may have on their access to specific treatment programs. Also here, adaptations have to be made where possible and more pilot studies need to be conducted in order to evaluate the feasibility and acceptability for OABD of already-existing treatment programs in the younger adult BD population.

2. Including more information than only clinical symptomatology is important in order to draw conclusions about the current state of the OABD patient

Despite information about current symptomatology, information about other aspects of functioning is important in order to offer appropriate treatment. We found that more depressive symptomatology is associated with worse daily functioning (**chapter 2**), but even after clinical remission, functional remission is not always present. And with age, functioning may become further decreased due to increased somatic burden and loss of social contacts. More information is needed than just information about the current mood symptoms, in order to draw conclusions about the current state of the OABD patient. Clinicians need to keep in mind that functioning includes multiple domains and that these domains are also interrelated. As our findings show, OABD exhibit dysfunction in several domains (**chapter 2,3,4 & 5**), such as social functioning and cognitive functioning (**chapters 4 & 5**). It is therefore important to be aware of the different functioning domains and to include these domains in clinical practice. The FAST-O (**chapter 3**) can be used as an efficient assessment method in order to draw a picture of the current level of functioning of the OABD patient. Functioning should therefore be considered as a valuable source of information to make statements about the current state of the patient.

3. Although it is a distinct and complex group, therapists should not be demoralized when treating OABD

OABD are a distinct group, with many aspects that need to be taken into account. However, therapists should not be demoralized when treating OABD. Although the course in OABD is often regarded as being capricious, even after a major life-event (COVID-19 pandemic), our group experienced less psychiatric symptoms when compared to three years before (**chapter 7**) and also in our earlier study (**chapter 6**) we found that at three-year follow-up, the majority of our participants did not experience recurrence of mood symptoms. Traditionally, BD was merely a psychiatric disorder treated by psychiatrists and medical doctors. However, over the last years, attention has risen for the implementation of psychological interventions in BD. Our findings show that already existing treatment programs, developed for younger adult BD patients, can be applied to OABD if inclusion criteria are carefully reconsidered (**chapter 9 & 10**). Up until this day, many treatment programs that are developed for the treatment of mood symptoms have not been adjusted for, or studied in OABD. This provides the opportunity to further investigate effective treatment strategies for this group. Findings in this thesis illustrate that there is potential in psychological treatments for OABD, but that future research in order to further adapt these treatment strategies is necessary.

# FUTURE RESEARCH

***Including a control group***

Most studies in this thesis only included OABD patients and analyses are mainly based on within-group differences. As mentioned before, also non-pathological aging is accompanied by changes that can lead to dysfunction in several areas of daily life. By only studying within-group characteristics in OABD, it remains unclear whether the observed findings are due to pathological aging, and thus merely an integral element of OABD, or whether these findings are also observed older adults without a psychiatric diagnosis. Therefore, it is necessary in future research to include control groups in order to draw conclusions about the process of aging in OABD.

***Combining different measures***

In this thesis, it was found that different sources of information can provide different dimensions of knowledge. For instance, we have found that there was a difference in the association between cognitive functioning and qualitative and quantitative measures of social functioning (**chapter 5**) and that these different measures were not interrelated. This illustrates the limitations of using merely quantitative measures in order to draw conclusions about characteristics in OABD. We also found (**chapter 2**) that it is possible to harmonize different depression scales into ordinal categories without losing statistical power. Besides the fact that all instruments used in this thesis are validated, the measures on social and psychological factors in this thesis still are an oversimplification of actual complex processes. Regarding the relative limited amount of research in OABD and the complexity of the phenotype, all available information should be used. Therefore, future research should include multiple sources of information and should combine these sources in order to draw a multidimensional picture of the OABD group.

***Psychological treatment strategies***

This thesis shows that there is potential in psychological treatment strategies for OABD (**chapters 9 & 10**). But up until now, psychological treatment is not used frequently in this group. However, treatment programs exist that were originally developed for the younger adult BD group, but have not been studied in OABD. For instance, studies on cognitive behavioral therapy (CBT) are limited in OABD. Results of CBT trials in younger adult BD patients have been mixed. A large RCT supports its use for acute bipolar depression[32] and efficacy of CBT in relapse prevention was observed in one RCT[33], but not in another larger RCT[34]. A promising new direction in CBT has been established by a pilot study of "recovery-focused CBT", with evidence of reduction of relapse in the intervention group[35]. This thesis shows that by conducting pilot studies, already developed treatment programs can be evaluated by their feasibility and

acceptability in the older patient population. Due to this gap in knowledge, there is still a lack of evidence for psychological treatment strategies in OABD whereas this is necessary for proper implementation in clinical practice. During the clinical interviews that were conducted for the DOBi-cohort, participants often mentioned experiences in their past that were traumatizing to them. Due to the clinical phenotype of OABD, patients often experience many episodes that can have a major impact on them, i.e. actions they have taken during manic episodes, stigma, reactions from family and friends and hospitalizations. These experiences might make participants vulnerable for recurrence. Therefore, future research should include a component of trauma treatment in this group.

***Resilience in OABD***

OABD knows a clinical course in which mood episodes frequently occur and most patients have been coping with these episodes for several years. However, despite these mood episodes and a decrease of daily functioning, patients seem to have developed their ways to cope with these circumstances. In order to learn more about how coping mechanisms and resilience in this group, future research should also focus on how participants stay resilient. Valuable information can be found by studying resilience in the group that does not experience recurrence, but also in the group that does experience recurrences and thereafter recovered. In order to do so, qualitative measurements should be used in order to create a greater understanding of resilience in this group. So besides focusing on understanding the pathology in this group, also a focus on the non-pathological aspects such as resilience, is necessary in order to expand the knowledge of OABD.

***Long-term outcomes of COVID-19***

Not only the indirect effects of the COVID-19 pandemic, such as disruption of daily routines and social isolation, but also a COVID-19 infection itself can have an impact on the mental health of patients. After a COVID-19 infection, cognitive dysfunction is reported by affected individuals, such as sustained memory impairments and executive dysfunction, including short-term memory loss, concentration problems, word-finding problems and impaired daily problem-solving[25,36]. OABD patients already show inter-episode cognitive dysfunction (**chapter 4**), and a COVID-19 infection might have additional negative effects. Since cognitive functioning is essential for accomplishing daily tasks, and thus for maintaining independency at an older age, it is important to gain more knowledge about the possible effects of a COVID-19 infection. In order to do so, OABD patients needs to be followed and neuropsychological assessments need to be frequently repeated. Patients that have experienced a COVID-19 infection should be compared with patients that did not experience a COVID-19 infection. Up until now, most studies have been focusing on the short-term outcomes of COVID-19, both direct

and indirect. However, it was found in younger adults that self-reported mental health problems still have not returned to pre-pandemic levels[25], emphasizing the importance of monitoring vulnerable patients even after the world is gaining control over COVID-19.

## IMPACT AND INFORMATION FOR PATIENTS AND THEIR LOVED ONES

OABD patients have many mood episodes, both depressive and manic. But also in between episodes, patients have problems in their daily functioning, cognitive functioning and physical health. These different areas also influence each other in their turn, making the disorder even more complex. For instance, it can become more and more difficult to maintain friendships when you are experiencing mobility problems or when it gets more difficult to remember social appointments. Therefore, it is important to give attention to functioning in OABD, because recovery is more than the absence of mania or depression. It can be hard for doctors or psychologists to estimate how the patient is doing in daily life, because most questionnaires or other instruments are not made for older patients. For instance, they often involve a lot of questions about work. To solve this problem, this thesis shows a new method to quickly estimate functioning in OABD. We also looked into what influences the entering of a new mania or depressive episode in OABD. This is important, because when we understand the disorder more, we can help patients faster and better. Eventually, we hope that we know exactly what to advise patients in order to prevent a new depressive or mania episode or what to do when this episode is already present. This thesis also contains two new treatment programs for OABD, because we have to keep searching for new ways to treat OABD patients and to look further than just the use of medication.

## CONCLUDING REMARKS

All in all, this thesis shows the population of OABD is a distinct and complex group. However, with the appropriate adjustments, currently existing diagnostic instruments and treatment strategies can be adapted in order to be used in the OABD group. There is still a lot unknown in the OABD group, but results show that progress can be gained in this field of research. In science, we are always searching for characteristics that reflect a whole group and finding treatment strategies that work for the majority of patients. However, as scientist-practitioners, we often find ourselves in a conflict. On the one hand, we strive to see each patient as a unique individual, whereas on the other hand, we try to find treatment strategies that work for the majority of patients. Since OABD patients show great variability in clinical phenotype, it is always important to not blindly follow findings from treatment studies or guidelines and to try to never lose sight of the individual patient.

Last, mood symptoms are not just an outcome measure but they are also an independent variable. They set in motion different processes in the lives of patients, and leave their scars. Therefore, we should not ignore the influence that the classification of BD has on an individual's life. At the same time, we should also seize the opportunity to learn how these individuals cope with the sometimes unpredictability of recurrence of mood symptoms. For the realization of this thesis, I have seen many OABD patients and it was fascinating to hear their stories and to learn how they have coped with the affective episodes and their aftermaths. The group of OABD is growing, and knowledge needs to be further expanded in order to improve inter-episodic functioning and treatment in OABD. It is time to move towards a more comprehensive approach to the disorder and to shift our focus towards more psychological and functional treatment approaches.

"*The more you know, the more you realize you don't know"* – Aristotle

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# 11

# Appendices

# NEDERLANDSE SAMENVATTING

## Balanceren tussen hoog en laag: Diagnostiek, begrijpen en behandeling van terugval bij ouderen met een bipolaire stoornis.

In dit proefschrift staan bevindingen beschreven van onderzoek naar diagnostiek, werkingsmechanismen en behandeling van ouderen met een bipolaire stoornis (OABD). Het doel van dit proefschrift is drieledig geweest. Ten eerste is getracht de kennis te verbreden met betrekking tot de diagnostiek en meetmethoden welke gebruikt worden bij OABD. Hiervoor hebben we onderzocht of verschillende instrumenten om depressie te meten geharmoniseerd konden worden om zo grotere datasets te creëren. Vervolgens hebben we de betrouwbaarheid en validiteit van een nieuw meetinstrument, de 'Functioning Assessment Short Test voor Ouderen' (FAST-O) onderzocht. Daarna hebben we cognitief functioneren in OABD vergeleken met cognitief functioneren bij ouderen met een depressie en een gezonde controlegroep. Het tweede doel van dit proefschrift was om de kennis te vergroten van het klinische fenotype van OABD en de onderlinge interacties. Hiervoor hebben we eerst de relatie tussen cognitief en sociaal functioneren in OABD onderzocht. Vervolgens hebben we gekeken naar de invloed van sociale, psychologische en cognitieve factoren op het klinisch beloop in OABD. Daarna hebben we psychiatrische symptomen bij OABD tijdens de COVID-19 pandemie onderzocht. Ten slotte hebben we gekeken naar het beloop van deze psychiatrische symptomen tijdens de eerste zes maanden van de COVID-19 pandemie. Ons derde doel was om de haalbaarheid en aanvaardbaarheid van nieuwe behandelinterventies voor OABD te toetsen. We hebben hiervoor eerst een groepsinterventie bestudeerd voor milde cognitieve problemen in OABD, waarna we ook een groepsinterventie hebben bestudeerd voor Interpersoonlijke en Sociaal Ritme Therapie (IPSRT) voor patiënten met terugkerende stemmingsklachten.

### SAMENVATTING VAN DE BELANGRIJKSTE BEVINDINGEN

#### *Diagnostiek*

In **hoofdstuk 2** hebben we associaties vergeleken tussen categorische en continue maten van depressie en het globaal functioneren in een grote dataset van OABD om zo te bestuderen of verschillende ernstmaten van depressie geharmoniseerd kunnen worden om zo een grote dataset te creëren. In de "Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD)" worden de 17-item "Hamilton Depression Scale (HAM-D)", "Montgomery Asberg Depression Rating Scale (MADRS)" of de "Centter for Epidemiological Studies Depression Scales (CES-D)" gebruikt om huidige depressieve symptomen te meten en de "Global Assessment of Functioning (GAF)" wordt gebruikt om huidig niveau van functioneren te meten. Data werden geharmoniseerd vanuit acht OABD studies ($n$ = 582). Effectmaten en verklaarde variantie van de categoriale maat in de totale groep was hoger dan zowel de categoriale als de continue maat in de

CES-D subgroep, hoger dan de categoriale maat, maar lager dan de continue maat in de HAM-D subgroep en lager dan zowel de categoriale als de continue maat in de MADRS subgroep. Gevonden werd dat associaties slechts enigszins groter waren voor de continue maat dan voor de categoriale maat van de depressieschalen. Om deze reden kan geconcludeerd worden dat het harmoniseren van verschillende depressieschalen naar ordinale categorieën voor het uitvoeren van analyses uitvoerbaar is, zonder te veel verlies van 'statistical power'.

In **hoofdstuk 3** hebben we een aangepaste versie van de "Functioning Assessment Short Test" (FAST) voor ouderen gevalideerd (de FAST-O). De originele FAST is ontwikkeld om het probleem op te lossen dat veel vaak gebruikte instrumenten er niet goed in slagen om psychosociaal functioneren bij patiënten met een bipolaire stoornis (BD) accuraat te meten. Echter is de originele FAST niet goed toepasbaar bij ouderen, door aanwezigheid van het domein van 'beroepsmatig functioneren'. We hebben de items in dit domein vervangen door items die het 'maatschappelijk functioneren' meten. We vonden dat de interne structuur van de FAST-O, gemeten door een 'confirmatory factor analysis', gelijk was aan de interne structuur van de interne structuur van de originele FAST. De interne consistentie was excellent. De concurrerende validiteit was laag, maar significant, wanneer er gekeken werd naar correlaties van de "Social and Occupational Functioning Assessment Scale" (SOFAS). De FAST-O was in staat om onderscheid te maken tussen euthyme en symptomatische OABD-patiënten. Om deze reden is geconcludeerd dat de FAST-O sterke psychometrische kwaliteiten heeft. Gebaseerd op onze bevindingen kan geconcludeerd worden dat de FAST-O een korte, efficiënte manier is om de meer globale maten of uitgebreide testbatterijen te vervangen om het dagelijks functioneren van oudere psychiatrische patiënten op een betrouwbare en valide manier te meten.

In **hoofdstuk 4** hebben we het cognitief functioneren in OABD vergeleken met cognitief functioneren bij ouderen met een depressie (LLD) en een gezonde controlegroep (HC). We hebben hun cognitief functioneren vergeleken aan de hand van verschillende neuropsychologische testen, verdeeld in vier domeinen: episodisch geheugen, verwerkingssnelheid, interferentie en werkgeheugen. Onze bevindingen lieten zien dat OABD- en LLD-patiënten slechter cognitief functioneren dan HC, waarbij OABD het grootste disfunctioneren laat zien op alle cognitieve domeinen, behalve bij interferentie inhibitie. Deze verschillen bleven significant na het controleren voor het effect van ernst van depressieve symptomen op het moment van testen. Deze bevindingen suggereren dat het cognitief functioneren slechter is in OABD, maar dat dezelfde domeinen zijn aangedaan als bij LLD. Dit verschil kon niet volledig verklaard worden door de ernst van de depressieve symptomen.

***Begrijpen***

In **hoofdstuk 5** hebben we de relatie tussen cognitief en sociaal functioneren in OABD onderzocht. We hebben verschillende domeinen van cognitief functioneren geïncludeerd en hebben de associatie met verschillende aspecten van sociaal functioneren bestudeerd. We vonden dat het algemeen sociaal functioneren, het aantal betekenisvolle contacten en sociale participatie niet onderling gerelateerd waren. Ook vonden we dat het algemeen cognitief functioneren, leren en geheugen en executief functioneren positief gerelateerd waren met het algemeen sociaal functioneren. Er werden geen associaties gevonden tussen cognitief functioneren en sociale participatie of het aantal betekenisvolle contacten. Ernst van de depressie en ziekteduur waren geen significante effectmoderatoren.

In **hoofdstuk 6** hebben we gefocust op sociale, psychologische en cognitieve factoren welke mogelijk geassocieerd zijn met terugval bij OABD. We gebruikten hierbij longitudinale data. De sociale factoren bestonden uit partner status, ouderstatus, algemeen sociaal functioneren en sociale steun. De psychologische factoren bestonden uit verschillende copingstijlen en cognitieve factoren bestonden uit het cognitief functioneren in de domeinen aandacht, leren/geheugen, executief functioneren en verbale vloeiendheid. We vonden geen significante associaties tussen de sociale, psychologische en cognitieve factoren en het krijgen van een terugval tijdens de driejarige follow-up periode. Echter waren de participanten in de terugvalgroep wel jonger, vaker vrouw en hadden minder vaak kinderen. Onze resultaten suggereren dat resultaten uit de jongere volwassene groep niet per definitie hetzelfde zijn voor OABD-patiënten.

In **hoofdstuk 7** hebben we gekeken naar factoren die geassocieerd waren met psychiatrische symptomen in OABD-patiënten tijdens de eerste maand van de COVID-19 pandemie. Tijdens de eerste maand van de COVID-19 pandemie, werd vooral aan ouderen geadviseerd om zoveel mogelijk thuis te blijven en om sociale contacten te beperken. Dit gaf ons de unieke mogelijkheid om factoren te bestuderen die mogelijk gerelateerd zijn aan terugval, tijdens het meemaken van deze gemeenschappelijke levensgebeurtenis. We vergeleken factoren, welke drie jaar voor de COVID-19 pandemie gemeten waren, met factoren die tijdens de pandemie gemeten werden. We vonden dat participanten minder psychiatrische symptomen ervoeren tijdens COVID-19 wanneer dit werd vergeleken met drie jaar hiervoor. Er was geen verschil in eenzaamheid tussen COVID-19 en drie jaar ervoor. Cross-sectioneel vonden we dat het hebben van kinderen, meer gevoelens van eenzaamheid, een lager gevoel van mastery, een meer passieve copingstijl en meer neuroticisme geassocieerd waren met meer psychiatrische symptomen tijdens COVID-19.

In **hoofdstuk 8** hebben we het beloop van psychiatrische symptomen bij OABD-patiënten tijdens de eerste zes maanden van de COVID-19 pandemie bestudeerd. We vonden dat depressieve, manische en angstsymptomen toenamen tijdens de eerste zes maanden van de pandemie. 'Mastery' was een factor welke interacteerde met het beloop van depressie- en angstsymptomen. Participanten met een hoger niveau van mastery ervoeren een grotere toename van symptomen dan participanten met een lager niveau van mastery, maar ervoeren nog steeds minder symptomen dan participanten met een lager niveau van mastery. Eenzaamheid interacteerde niet met het beloop van de psychiatrische symptomen. We vonden dat OABD-patiënten veerkrachtig waren in de eerste maanden van de COVID-19 pandemie. Echter namen depressieve, manische en angstsymptomen toe naarmate de pandemie voortduurde.

***Behandeling***

In **hoofdstuk 9** hebben we de uitvoerbaarheid en tevredenheid van een groepsinterventie voor milde cognitieve problemen in OABD onderzocht. Het behandelprogramma, genaamd "Braintrain" bestond uit een combinatie van cognitieve training en fysieke activiteit, en is eerder bestudeerd in jongere volwassenen met BD. Inclusie was mogelijk wanneer participanten objectief waarneembare cognitieve problemen lieten zien en wanneer zij in staat waren om 30 minuten aan een stuk door te wandelen. Het eerste doel van "Braintrain" was om de uitvoerbaarheid en patiënttevredenheid te evalueren van dit behandelprogramma voor OABD. Het tweede doel was om mogelijke positieve effecten van het behandelprogramma op cognitief functioneren, fysieke kracht, sociale participatie en stemmingssymptomen in kaart te brengen. De interventie werd aan drie groepen gegeven en in totaal werden er 18 participanten geïncludeerd. Participanten mochten niet meer dan drie sessies missen en de meeste participanten slaagden erin om hun wekelijkse huiswerk bij te houden, al was dit voor sommigen moeilijk. Het sociale aspect werd het meest gewaardeerd door de participanten. Het was moeilijk om participanten te includeren gebaseerd op hun objectief cognitief functioneren, omdat we zagen dat veel participanten met verminderd cognitief functioneren ook een slechtere fysieke conditie hadden. Om zorg op maat te kunnen garanderen voor OABD-patiënten, is een grotere variabiliteit en flexibiliteit in fysieke interventies nodig.

In **hoofdstuk 10** hebben we de uitvoerbaarheid en aanvaardbaarheid van een Interpersoonlijke en Sociaal Ritme Therapie (IPSRT) groepsbehandeling onderzocht. 36 patiënten met ofwel een diagnose van bipolaire stoornis ofwel een depressieve stoornis werden geïncludeerd. IPSRT was ontworpen om het zelfvertrouwen van patiënten met stemmingsstoornissen te vergroten door het stabiliseren van onderliggende verstoringen in circadiane ritmes, als aanvulling op strategieën uit de interpersoonlijke psychotherapie. IPSRT was nog niet onderzocht in een groepsformat

waarbij zowel patiënten met een depressieve stoornis als patiënten met een bipolaire stoornis werden geïncludeerd. We vonden dat het uitvoerbaar en aanvaardbaar was om twee keer per week een IPSRT- groepssessie te implementeren voor deze groep. Daarbij vonden we ook dat de kwaliteit van leven was verbeterd, drie maanden na afronding van de behandeling.

## INTEGRATIE VAN DE BELANGRIJKSTE BEVINDINGEN

### *Diagnostiek*

De classificatie van de bipolaire stoornis is vooral gebaseerd op de klinische presentatie, waarbij de eerste hoofdstukken van dit proefschrift laten zien dat de classificatie van de bipolaire stoornis uitgebreider en veelomvattender is dan alleen de aanwezigheid van stemmingsepisoden. Terwijl behandeling veelal vooral gericht is op de remissie van stemmingssymptomen, wordt de focus op functionele aspecten vaak verwaarloosd. Gevonden werd (**hoofdstuk 3**) dat de aanwezigheid van huidige depressieve symptomen sterk gerelateerd is aan dagelijks functioneren, ondanks het gebruik van verschillende instrumenten om deze depressie te meten. Functioneel herstel is niet altijd aanwezig, zelfs wanneer de stemmingssymptomen wel in remissie zijn. Functioneren bij de bipolaire stoornis is een multifactorieel construct, waarbij OABD-patiënten disfunctioneren in verschillende domeinen laten zien, waaronder cognitief functioneren (**hoofdstuk 4**). Cognitief functioneren is belangrijk voor ons dagelijks functioneren, waarbij het nodig is om activiteiten te plannen, dingen te onthouden, onze aandacht te richten en te wisselen tussen verschillende taken. Er werd gevonden dat OABD-patiënten slechter cognitief functioneren lieten zien dan oudere patiënten met een depressie (LLD) en de gezonde controlegroep (HC). Ook konden verschillen in cognitief functioneren niet volledig verklaard worden door de huidige depressieve symptomen (**hoofdstuk 4**), en is het dus waarschijnlijk dat deze ook aanwezig zijn wanneer stemmingssymptomen in remissie zijn. Geschat wordt dat ongeveer 40% van de OABD-patiënten cognitief disfunctioneren laat zien en dat cognitief functioneren mogelijk verslechtert door het beloop van de bipolaire stoornis. In OABD-patiënten kan het functioneren nog meer verslechteren als resultaat van verschillende factoren, zoals een afname van de sociale netwerkgrootte en verminderde mobiliteit. Onderzoekers en clinici zijn in toenemende mate niet alleen gefocust op klinische remissie, maar prioriteren ook steeds meer het functioneel herstel en welzijn. Echter, het maken van een betrouwbare inschatting van het huidige niveau van functioneren blijft een opgave. Huidige instrumenten die vaak worden gebruikt hiervoor, zoals de "Global Assessment of Functioning Scale" (GAF) zijn niet volledig toepasbaar in de oudere patiëntenpopulatie, gezien delen van deze schalen vaak betrekking hebben op het beroepsmatig functioneren. Om het huidige niveau van functioneren te meten, hebben wij om deze reden de "Functioning Assessment Short Test" (FAST) aangepast naar een versie welke gebruikt kan worden bij OABD-patiënten (FAST-O; **hoofdstuk 3**). Om dit

te doen, hebben we de sectie van 'beroepsmatig functioneren' vervangen door het domein 'maatschappelijk functioneren' om de toepasbaarheid in de ouderenpopulatie te vergroten. Door het bestuderen van de betrouwbaarheid en validiteit van dit instrument, hebben we gevonden dat de FAST-O een korte, efficiënte manier is om globale screeners of uitgebreide testbatterijen te vervangen bij OABD (**hoofdstuk 3**). De bevindingen in **hoofdstuk 2, 3 en 4** laten zien dat OABD specifiek disfunctioneren laten zien in verschillende domeinen en dat met gepaste aanpassingen, bestaande instrumenten gebruikt kunnen worden om een inschatting te maken van het huidige niveau van functioneren van het individu. Deze bevindingen benadrukken het belang van het combineren van meerdere functionele domeinen in de klinische praktijk.

***Begrijpen***

Het klinische fenotype van OABD kent een grote variabiliteit en onderling gerelateerde factoren die de complexiteit van de stoornis benadrukken. Gevonden werd dat OABD meer cognitieve problemen laten zien dan LLD en HC (**hoofdstuk 4**) en dat cognitief functioneren gerelateerd is aan andere aspecten van functioneren, bijvoorbeeld aan het sociaal functioneren (**hoofdstuk 5**). We vonden dat verschillende maten van kwalitatief en kwantitatief sociaal functioneren niet onderling gerelateerd waren aan elkaar. Hierbij vonden we dat alleen een kwalitatieve maat van sociaal functioneren was geassocieerd met het cognitief functioneren (**hoofdstuk 5**). Dit laat zien dat vooral de kwaliteit van sociale interacties beïnvloed lijkt te worden door cognitief disfunctioneren en niet alleen de kwantiteit van sociale relaties. Tot nu toe is er in OABD vooral cross-sectioneel gekeken naar deze factoren en blijft het onduidelijk welke factoren nu gerelateerd zijn aan terugval in deze groep. Voorheen werd in het DOBi-cohort gevonden, dat er geen associaties waren tussen terugval in OABD en verschillende klinische voorspellers, zoals somatische ziekten, leeftijd bij de eerste episode of het hebben van voornamelijk depressieve of manische episoden. In jongere volwassenen werden er associaties gevonden tussen verslechterd sociaal functioneren, het niet hebben van een vaste partner, meer emotionele en vermijdende coping en verminderd cognitief functioneren en een korte tijd tot terugval en meer depressieve episoden. Om deze reden hebben we onze focus verbreed en hebben we de associatie tussen verschillen sociale, psychologische en cognitieve factoren en terugval na drie jaar (**hoofdstuk 6**). We vonden geen significante associaties, maar we vonden wel dat 37.5% van alle participanten één of meer terugvallen had meegemaakt en dat participanten die terugvielen jonger waren, vaker vrouw waren en minder vaak kinderen hadden. In het begin van 2020, startte de COVID-19 pandemie en verschillende maatregelen werden ingesteld door de Nederlandse overheid om de verspreiding van het virus te beperken. In de eerste zes maanden van de pandemie hebben we terugval in het DOBi-cohort bestudeerd tijdens het meemaken van een collectieve levensgebeurtenis (**hoofdstuk 7**), waarbij zij dus min of meer aan dezelfde

omstandigheden werden blootgesteld. Onze participanten lieten een verlaging van stemmingssymptomen zien tijdens de eerste maand van de pandemie, wanneer deze symptomen vergeleken werden met drie jaar voor de pandemie. Dit verschilde van bevindingen in de jongere volwassenen populatie met een bipolaire stoornis, waarbij gezien werd dat er een verhoging was van manische symptomen. Een hogere leeftijd leek dus een beschermende factor te zijn. Ook andere studies lieten zien dat adolescenten en jongere volwassenen disproportioneel meer werden geraakt door gevolgen van de pandemie, vergeleken met jongere kinderen en oudere volwassenen. Verwacht wordt dat dit een resultaat is van verschillende negatieve gedragsmatige en sociale veranderingen. Echter was er ook een subgroep binnen onze participanten welke wel een verhoging van stemmingssymptomen liet zien tijdens COVID-19. Hierbij vonden wij cross-sectioneel dat een verhoging van stemmingssymptomen geassocieerd was met het niet hebben van kinderen, meer gevoelens van eenzaamheid, een verminderd gevoel van 'mastery', een meer passieve coping stijl en een hogere score op de persoonlijkheidstrek 'neuroticisme'. Wanneer we longitudinaal keken naar het beloop van stemmingssymptomen tijdens COVID-19, vonden we dat stemmingssymptomen over tijd toenamen (**hoofdstuk 8**). Het gevoel van 'mastery' speelde een belangrijke rol in het beloop van deze symptomen, waarbij participanten met een groter gevoel van mastery, een grotere toename van stemmingssymptomen lieten zien tijdens de eerste drie maanden van de pandemie. Echter, ondanks een grotere toename van symptomen, hadden participanten met een groter gevoel van mastery nog steeds minder last van stemmingssymptomen dan participanten met een verminderd gevoel van mastery. Dit indiceert dat het gevoel van mastery mogelijk een belangrijke rol kan spelen bij veerkracht in deze groep. Ook al wordt het beloop van BD op latere leeftijd vaak gezien als grillig, liet onze groep minder stemmingssymptomen zien tijdens de COVID-19 pandemie vergeleken met drie jaar ervoor (**hoofdstuk 7**). Ook in onze eerdere studie (**hoofdstuk 6**) vonden we dat na drie jaar, 60.9% van onze participanten geen terugval hadden ervaren en dat 28.1% van alle participanten slechts één terugval had ervaren.

***Behandeling***

De laatste jaren is er steeds meer aandacht gekomen voor het ontwikkelen en implementeren van psychologische behandelingen voor de bipolaire stoornis, bijvoorbeeld in de vorm van cognitieve therapieën en 'family-focused' therapieën. De meeste van deze therapieën zijn echter vaak ontwikkeld voor jongere patiënten en hierom zijn zij niet altijd passend voor OABD. In het eerste gedeelte van dit proefschrift, is laten zien dat zelfs wanneer de symptomen in remissie zijn, er sprake is van verminderd functioneren in andere gebieden (**hoofdstuk 2**), bijvoorbeeld op het gebied van dagelijks functioneren (**hoofdstuk 3**), sociaal functioneren (**hoofdstuk 5**) en cognitief functioneren (**hoofdstuk 4**). Dus naast het focussen op klinische remissie, bijvoorbeeld door het gebruik van medicatie, dienen ook andere aspecten

van OABD mee te worden genomen in de behandeling om zo functionele remissie te bewerkstelligen. Gezien OABD-patiënten significant verminderd cognitief functioneren laten zien (**hoofdstuk 4**), zou een eerste belangrijke focus voor behandeling kunnen zijn om het cognitief functioneren te verbeteren. Om deze reden, werd een bestaand behandelprogramma aangepast voor de oudere patiëntenpopulatie en vonden we dat het aanpassen van een studieprotocol voor OABD ook zijn moeilijkheden kent (**hoofdstuk 9**). Inclusiecriteria moeten bijvoorbeeld heroverwogen worden en kunnen niet zomaar worden overgenomen uit onderzoek in de jongere patiëntenpopulatie. We vonden dat inclusie voor dit behandelprogramma, bestaande uit cognitieve remediatie en fysieke activiteiten voor participanten met objectief cognitief disfunctioneren, moeilijk was. De meeste participanten die voldeden aan dit inclusiecriterium, voldeden niet aan het inclusiecriterium dat zij minimaal 30 minuten aan een stuk door moesten kunnen wandelen (**hoofdstuk 9**). Echter, inclusie hoeft niet altijd moeilijk te zijn in de ouderenpopulatie. In onze tweede pilotstudie (**hoofdstuk 10**), was ons doel om participanten te includeren met een verscheidenheid aan leeftijden, waarbij we vooral participanten van 60 jaar en ouder konden includeren. In deze studie hebben we de therapie 'IP-SRT' toegediend bij een gemixte groep participanten met ofwel een bipolaire stoornis ofwel een unipolaire depressie. Deze interventie was uitvoerbaar en het was haalbaar om twee sessies per week te geven, waar dit voorheen slechts eens per week werd gedaan. Deze psychologische behandeling resulteerde in een hoge tevredenheid onder participanten, lage uitvalpercentages en een verbetering van de kwaliteit van leven (**hoofdstuk 10**). Bevindingen uit deze studies laten zien dat bestaande studieprotocollen niet zonder meer gebruikt kunnen worden in de oudere patiëntenpopulatie, maar dat een secure heroverweging van het materiaal en de in- en exclusiecriteria van groot belang zijn. Daarbij moet er vooral gekeken worden naar populatie-specifieke criteria, bijvoorbeeld met betrekking tot de huidige fysieke conditie en het cognitief functioneren.

## METHODOLOGISCHE OVERWEGINGEN

### *Sterke punten en beperkingen*

Behalve de sterke punten en de beperkingen die in ieder individueel paper aan bod komen, zijn er ook verschillende algemene punten welke aandacht verdienen.

Cohortstudies

Resultaten in dit proefschrift zijn veelal gebaseerd op cohortsudies: DOBi, NESDO en de studies welke geïncludeerd zijn in het GAGE-BD consortium. Door de relatief grote geïncludeerde groepen, konden we hierdoor een breed scala aan data verzamelen. Dit gaf ons de kans om de interactie tussen verschillende factoren in OABD te onderzoeken en om deze te vergelijken met data vanuit andere OABD-studies over de hele wereld. Echter, cohortstudies kennen ook beperkingen. In de meeste van de gebruikte

studies, werden de variabelen cross-sectioneel gemeten. Om deze reden kunnen er geen conclusies worden getrokken op het gebied van de causaliteit van onze bevindingen. Verder kan er binnen een cohortstudie een 'vaststaand' of een 'dynamisch' onderzoeksdesign gebruikt worden. DOBi kent een vaststaand studiedesign. Een groot nadeel hiervan is dat de onderzoeksgroep kleiner kan worden, door het uit beeld raken van een deel van de participanten. Dit is nog eens extra het geval bij de oudere patiëntenpopulatie. Dit kan een vertekening in de onderzoeksbevindingen opleveren.

Specifieke populatie

De meeste geïncludeerde studies hebben hun dataverzameling in Nederland verricht, maar in **hoofdstuk 2** werden er ook participanten geïncludeerd vanuit andere delen van de wereld. Echter, onze conclusies hebben vooral betrekking op "WEIRD" participanten (wit ('white'), geschoold ('educated'), geïndustrialiseerd ('industrialized'), rijk ('rich') en democratisch ('democratic')). Ook hebben we vooral participanten geïncludeerd welke in zorg zijn in de specialistische GGZ op het moment van inclusie. Het zou zo kunnen zijn dat er patiënten met BD zijn welke geen frequente, specialistische zorg nodig hebben of welke alleen door hun huisarts worden gezien. Om deze reden zou het zo kunnen zijn dat onze groep een meer ernstige groep representeert. Dit wordt ook wel 'Slater's bedrog' genoemd, wat in deze context inhoudt dat patiënten die meer episoden hebben, waarschijnlijk overgerepresenteerd worden in een cross-sectionele steekproef. Aan de andere kant hebben wij ons gefocust op de oudere patiëntenpopulatie in onze studies. Bij het interpreteren van onze bevindingen moet daarom rekening gehouden worden dat er mogelijk sprake is van een 'gezonde overlever'-effect. Dit betekent dat individuen die eerder overlijden of die te ziek zijn om aan onderzoek deel te nemen, de bevindingen vertekenen naar de kant van ouderen met wie het relatief goed gaat. Al deze punten laten zien dat we een specifieke populatie hebben bestudeerd en dat enige voorzichtigheid geboden is bij het interpreteren van onze bevindingen.

Normale veroudering versus pathologische veroudering

In de meeste studies in dit proefschrift hebben we verschillende karakteristieken binnen populaties bestudeerd, vooral binnen de OABD-populatie. Maar ook in 'normale' veroudering hebben mensen te kampen met enorme veranderingen en aanpassingen in hun leven, bijvoorbeeld in het cognitief en dagelijks functioneren. Omdat we vooral hebben gefocust op psychiatrische patiëntenpopulaties, blijft het onduidelijk of onze bevindingen alleen gelden voor de OABD-populatie, of, en in welke mate, deze ook gelden in ouderen zonder een bipolaire stoornis. Het blijft dus onduidelijk of de gevonden associaties nu een resultaat zijn van normale veroudering, of dat ze passen bij pathologische veroudering. Om hier uitspraken over te kunnen doen, is het essentieel om controlegroepen te includeren in toekomstig onderzoek.

## KLINISCHE IMPLICATIES

De Nederlandse bevolking veroudert snel. Om deze reden zijn specifieke aanbevelingen voor het diagnosticeren en behandelen van OABD nodig. Gebaseerd op de bevindingen in dit proefschrift, kunnen verschillende klinische implicaties worden opgesteld.

1. OABD zijn een unieke groep en resultaten uit de jongere volwassenen patiëntengroep kunnen niet zonder meer worden overgenomen

Tot op heden is er relatief weinig aandacht voor de oudere patiëntenpopulatie, vergeleken met de jongere volwassenen patiëntenpopulatie. Het grootste deel van het onderzoek, diagnostische methoden en behandelstrategieën is ontwikkeld voor de jongere patiëntenpopulatie en worden vaak toch gebruikt voor oudere patiënten. Echter, dit proefschrift laat zien dat bevindingen in OABD verschillen van bevindingen bij jongere patiënten. Onze bevindingen laten zien dat factoren die geassocieerd zijn terugval in de jongere volwassenen groep, niet waren geassocieerd met terugval in OABD (**hoofdstuk 6**). Ook verschilden de resultaten welke tijdens de COVID-19 pandemie werden gevonden (**hoofdstuk 7 & 8**). Dit onderstreept het feit dat OABD een unieke groep vormen en dat resultaten uit de jongere volwassenen groep niet zonder meer gelden voor deze groep. Clinici moeten dus alert zijn op de verschillen tussen deze groepen en de bijbehorende andere focusgebieden tijdens de behandeling. De meeste meetinstrumenten zijn ontwikkeld voor jongere patiënten, waarbij sommige items niet bruikbaar zijn in de OABD-groep. Dit resulteert in het ontbreken van essentiële informatie bij bijvoorbeeld het huidig niveau van functioneren. Onze bevindingen impliceren dat meetinstrumenten beoordeeld moeten worden op hun bruikbaarheid en dat aanpassingen gedaan moeten worden waar mogelijk. Dit geldt ook voor de implementatie van behandelstrategieën welke effectief zijn bevonden in de jongere patiëntengroep. Clinici dienen zich ook bewust te zijn van de specifieke karakteristieken van de OABD-groep, zoals somatische comorbiditeit en cognitieve problemen, en welke impact deze karakteristieken hebben op de toegang tot bepaalde behandelprogramma's. Ook hier moeten aanpassingen gedaan worden waar mogelijk en dienen er meer pilotstudies gedaan te worden om de uitvoerbaarheid en haalbaarheid van bestaande behandelprogramma's te toetsen voor OABD.

2. Het includeren van meer informatie dan slechts klinische symptomatologie is belangrijk om de huidige staat van de OABD-patiënt te kunnen beoordelen



Ondanks informatie over de huidige symptomen is informatie over andere aspecten van het functioneren belangrijk om passende behandeling te kunnen bieden. We vonden dat meer depressieve symptomen geassocieerd zijn met slechter dagelijks functioneren (**hoofdstuk 2**). Er is echter niet altijd sprake van functionele remissie,

zelfs wanneer er wel sprake is van klinische remissie. Bij veroudering kan het dagelijks functioneren zelfs nog sneller verslechteren, door bijvoorbeeld meer somatische ziekten en een vermindering van sociale contacten. Er is dus meer informatie nodig dan alleen informatie over de huidige stemmingssymptomen, om conclusies te trekken over de huidige staat van de OABD-patiënten. Clinici dienen hierbij alert te zijn op het feit dat functioneren een multidimensionaal construct is, bestaande uit meerdere domeinen en waarbij deze domeinen ook elkaar onderling beïnvloeden. Onze bevindingen laten zien dat OABD verminderd functioneren laten zien op verschillende domeinen (**hoofdstuk 2,3,4 & 5**), zoals sociaal functioneren en cognitief functioneren (**hoofdstuk 4 & 5**). Het is om deze reden belangrijk om alert te zijn op de verschillende functionele domeinen en om deze domeinen ook onderdeel te laten zijn van de behandeling. De FAST-O (**hoofdstuk 3**) kan gebruikt worden als een efficiënte meetmethode om een beeld te schetsen van het huidig functioneren van de OABD-patiënt. Het huidig functioneren dient dus gezien te worden als een waardevolle bron van informatie om de huidige staat van de patiënt te beoordelen.

3. Ondanks dat het een unieke en complexe groep is, moeten behandelaren niet ontmoedigd moeten worden om OABD-patiënten te behandelen

OABD-patiënten vormen een unieke groep, waarbij veel verschillende aspecten in overweging dienen te worden genomen. Echter moeten behandelaren niet ontmoedigd worden bij het behandelen van deze groep. Al worden de klachten in de OABD-groep vaak gezien als grillig, zagen we zelfs na het meemaken van een grote levensgebeurtenis (de COVID-19 pandemie), dat onze groep minder stemmingssymptomen liet zien ten opzichte van drie jaar eerder (**hoofdstuk 7**). Ook in onze eerdere studie (**hoofdstuk 6**) zagen we dat na drie jaar, de meerderheid van onze participanten geen terugval had ervaren. Traditioneel gezien was de bipolaire stoornis vooral een psychiatrische stoornis welke behandeld werd door psychiaters en andere artsen. Echter is er de laatste jaren steeds meer aandacht gekomen voor het inzetten van psychologische interventies. Onze bevindingen laten zien dat bestaande behandelprogramma's welke ontwikkeld zijn voor jongere patiënten, ook toegepast kunnen worden bij OABD-patiënten wanneer er goed gekeken wordt naar de inclusiecriteria (**hoofdstuk 9 & 10**). Tot nu toe zijn er veel behandelprogramma's nog niet aangepast en onderzocht bij OABD-patiënten. Dit geeft ons de mogelijkheid om effectieve behandelstrategieën voor deze groep verder te onderzoeken. Bevindingen in dit proefschrift laten zien dat er potentie zit in psychologische behandelingen voor OABD, maar dat meer onderzoek nodig is om deze behandelingen toe te kunnen spitsen op deze specifieke groep.

## TOEKOMSTIG ONDERZOEK

***Het includeren van een controlegroep***

De meeste studies in dit proefschrift hebben alleen een groep van OABD-patiënten geïncludeerd en zijn dus vooral gebaseerd op verschillen binnen deze groep. Zoals eerder genoemd worden ook bij 'normale' veroudering veranderingen gezien welke kunnen leiden tot disfunctioneren op verschillende levensgebieden. Door alleen verschillen te bestuderen binnen de groep van OABD-patiënten, blijft het dus onduidelijk of de bevindingen nu het resultaat zijn van pathologische veroudering, en dus een integraal onderdeel van OABD, of dat deze bevindingen ook gezien worden bij ouderen zonder een psychiatrische diagnose. Om deze reden is het noodzakelijk om in toekomstig onderzoek ook controlegroepen te includeren en zo conclusies te kunnen trekken over het verouderingsproces in OABD.

***Combineren van verschillende metingen***

In dit proefschrift werd gevonden dat verschillende bronnen van informatie ook verschillende informatie opleveren. We vonden bijvoorbeeld dat er een verschil zat in de associatie tussen cognitief functioneren en de kwantitatieve en kwalitatieve maten van sociaal functioneren (**hoofdstuk 5**) en dat deze metingen niet onderling gerelateerd waren. Dit laat de beperkingen van het veelal gebruiken van alleen kwantitatieve maten zien om conclusies te trekken over werkingsmechanismen binnen OABD. We vonden ook (**hoofdstuk 2**) dat het mogelijk was om verschillende depressiematen te harmoniseren zonder het verliezen van te veel 'statistische power'. Ondanks dat alle gebruikte instrumenten in dit proefschrift gevalideerd zijn, zijn de metingen van sociale en psychologische factoren nog steeds een versimpeling van zeer complexe processen. Met in achtneming van het feit dat er relatief weinig onderzoek naar OABD beschikbaar is en de complexiteit van het fenotype, wordt duidelijk dat alle beschikbare informatie gebruikt zou moeten worden. Om deze reden is het belangrijk dat er in toekomstig onderzoek gebruik wordt gemaakt van verschillende informatiebronnen en dat deze informatie gecombineerd moet worden om zo een multidimensioneel beeld te kunnen vormen van de OABD-groep.

***Psychologische behandelstrategieën***

Dit proefschrift laat zien dat er potentie zit in psychologische behandelstrategieën voor OABD (**hoofdstuk 9 & 10**). Echter worden psychologische behandelingen nog niet frequent ingezet in deze groep. Er bestaan echter behandelprogramma's welke ontwikkeld zijn voor de jongere BD-groep, maar welke nog niet onderzocht zijn bij OABD. Er is bijvoorbeeld relatief weinig onderzoek gedaan naar de toepassing van cognitieve gedragstherapie (CGT) bij OABD. Resultaten van CGT-studies in jongere BD-patiënten zijn gemengd. Een grote RCT ondersteunt de inzet van CGT bij een acute bipolaire depressie en ook effectiviteit van CGT bij terugvalpreventie is gevonden in

een andere RCT. Dit laatste effect werd echter niet opnieuw gevonden in een grotere RCT. Een veelbelovende nieuwe richting in de CGT is laten zien in een pilotstudie welke gebruik maakt van "herstel-gefocuste CGT". Hierbij werd ook een vermindering van terugval geobserveerd. Dit proefschrift laat zien dat door het uitvoeren van pilotstudies, bestaande behandelprogramma's bestudeerd kunnen worden op de uitvoerbaarheid en haalbaarheid in de oudere patiëntenpopulatie. Door beperkt onderzoek op dit gebied, blijft er beperkt bewijs voor de effectiviteit van psychologische behandelmethoden in OABD terwijl dit noodzakelijk is voor een gedegen implementatie in de klinische praktijk. Tijdens de interviews welke gedaan werden in het DOBi-cohort, benoemden participanten veelal eerdere ervaringen welke zij als traumatiserend bestempelden. Gezien het klinische fenotype van OABD, hebben patiënten vaak veel episoden welke een grote impact op hen hebben. Bijvoorbeeld doordat zij dingen hebben gedaan tijdens hun manische episoden, stigma, reacties van familie en vrienden en verschillende opnamen. Deze ervaringen kunnen participanten kwetsbaar maken voor terugval. Toekomstige behandelmethoden zouden daarbij mogelijk ook gebruik kunnen maken van de inzet van een component van traumabehandeling bij deze groep.

***Veerkracht in OABD***

OABD kent een klinisch beloop waarbij stemmingssymptomen frequent voorkomen en de meeste participanten moeten al vele jaren met deze episoden om zien te gaan. Ondanks de terugkeer van stemmingssymptomen en een verminderd dagelijks functioneren, hebben patiënten hun eigen weg gevonden hoe om te gaan met deze omstandigheden. Om meer te leren over copingmechanismen en veerkracht in deze groep, zal toekomstig onderzoek zich ook moeten focussen op hoe participanten veerkrachtig blijven. Waardevolle informatie kan hierbij gevonden worden in het onderzoeken van de groep die niet terugvalt, maar ook in de groep die wel terugvalt en daarna weer herstelt. Om dit te bewerkstelligen, moeten kwalitatieve metingen worden ingezet om veerkracht in deze groep beter te kunnen begrijpen. Dus behalve het focussen op de pathologie in deze groep, moet er ook een focus zijn op niet-pathologische aspecten van deze groep, om zo de kennis over OABD te vergroten.

***Lange termijneffecten van COVID-19***

Niet alleen de indirecte effecten van de COVID-19 pandemie, zoals een verstoring van dagelijkse routines en sociale isolatie, maar ook een COVID-19 infectie zelf zou een impact kunnen hebben op de mentale gezondheid van patiënten. Na een COVID-19 infectie worden veelal cognitieve problemen gerapporteerd, zoals bijvoorbeeld geheugenproblemen en problemen in het executief functioneren. OABD-patiënten laten ook tussen episoden cognitieve problemen zien (**hoofdstuk 4**) en een COVID-19 infectie kan extra bijkomende negatieve effecten hebben. Aangezien cognitief functioneren noodzakelijk is voor het verrichten van dagelijkse taken en dus voor het

behouden van onafhankelijkheid op latere leeftijd, is het belangrijk om meer kennis te hebben over de mogelijke effecten van een COVID-19 infectie. Hiervoor is het nodig om OABD-patiënten te volgen, waarbij neuropsychologische testen frequent herhaald dienen te worden. Patiënten die een COVID-19 infectie hebben meegemaakt dienen vergeleken te worden met patiënten die dit niet hebben meegemaakt. Tot nu toe focussen de meeste studies zich op de korte termijneffecten van COVID-19, zowel direct als indirect. In jongere volwassenen werd gevonden dat zelf-gerapporteerde stemmingssymptomen nog steeds niet naar het niveau van voor de pandemie zijn teruggekeerd. Dit benadrukt het belang van het monitoren van kwetsbare patiënten, zelfs nadat de wereld de controle over COVID-19 aan het terugwinnen is.

## IMPACT EN INFORMATIE VOOR PATIËNTEN EN NAASTEN

OABD-patiënten hebben te kampen met vele stemmingsepisoden, zowel depressief als manisch. Maar ook tussen episodes, hebben veel patiënten problemen met hun dagelijks functioneren, hun cognitief functioneren en hun fysieke gezondheid. Deze verschillende gebieden beïnvloeden elkaar ook, waardoor de stoornis erg complex is. Het kan bijvoorbeeld steeds moeilijker worden om vriendschappen te onderhouden wanneer je minder mobiel bent of wanneer het moeilijker wordt om afspraken te onthouden. Daarom is het belangrijk om aandacht te hebben voor het functioneren bij OABD, omdat herstel meer is dan de afwezigheid van een manie of een depressie. Het kan moeilijk zijn voor dokters of psychologen om in te schatten hoe het nu echt gaat in het dagelijks leven van de patiënt, omdat de meeste vragenlijsten niet gemaakt zijn voor oudere patiënten. Ze bevatten bijvoorbeeld vaak veel vragen over werk. Om dit probleem op te lossen, is er in dit proefschrift een nieuwe manier bedacht om snel het dagelijks functioneren in te schatten bij OABD. Dit is belangrijk omdat wanneer we de stoornis beter begrijpen, we mensen ook sneller en beter kunnen helpen. Uiteindelijk hopen we dat we precies weten wat we patiënten moeten adviseren om een nieuwe depressieve of manische episode te voorkomen of wat we moeten doen wanneer er al sprake is van een terugval. Dit proefschrift bevat ook twee onderzoeken naar nieuwe behandelingen voor OABD, omdat we moeten blijven zoeken naar nieuwe manieren om patiënten met OABD te behandelen en verder te kijken dan alleen het gebruik van medicatie.

## CONCLUSIES

Dit proefschrift laat zien dat de OABD-groep een unieke en complexe groep is. Wanneer echter de juiste aanpassingen gedaan worden, kunnen bestaande diagnostische instrumenten en behandelprogramma's aangepast worden om zo ingezet te worden voor OABD-patiënten. Er is nog steeds veel onduidelijk over de OABD-groep, maar resultaten laten zien dat vooruitgang geboekt kan worden in dit onderzoeksveld. In de wetenschap zijn we altijd op zoek naar karakteristieken welke gelden voor een gehele

groep, of behandelmethoden die werken voor de meerderheid van de patiënten. Echter bevinden we ons als 'scientist-practitioners' vaak in een tweestrijd. Aan de ene kant willen we elke patiënt zien als een unieke individu, waarbij we aan de andere kant behandelstrategieën willen vinden die voor de grootste groep werken. Omdat OABD-patiënten een grote variabiliteit laten zien in hun klinische presentatie is het altijd belangrijk om niet blind de bevindingen uit behandelstudies of richtlijnen te volgen en dus nooit de individuele patiënt uit het oog te verliezen.

Stemmingssymptomen zijn niet slechts een uitkomstmaat, maar zij zijn ook een onafhankelijke variabele. Ze zetten verschillende processen in werking in het leven van de patiënten en laten zo hun sporen na. Om deze reden moeten we niet vergeten dat een classificatie van BD een grote impact kan hebben op het leven van het individu. Tegelijkertijd moeten we gebruik maken van de mogelijkheden om te leren hoe deze individuen omgaan met de onvoorspelbaarheid van de terugkeer van stemmingssymptomen. Voor het schrijven van dit proefschrift, heb ik vele OABD-patiënten gezien en was het fascinerend om hun verhalen te horen en te leren hoe zij hebben weten om te gaan met hun stemmingsepisoden en bijbehorende nasleep. De groep van OABD-patiënten groeit en de kennis over deze groep moet vergroot worden om inter-episodisch functioneren en behandeling te verbeteren. Het is tijd om naar een uitgebreidere benadering van de stoornis toe te werken en om onze focus te verleggen naar meer psychologische en functionele behandelbenaderingen.

*"Hoe meer je weet, hoe meer je weet wat je niet weet"* – Aristoteles

# ABOUT THE AUTHOR (CURRICULUM VITAE)

Melis Miene Orhan was born on October 2nd 1994 in Nijmegen, the Netherlands. She graduated from secondary school, at Kandinsky College in Nijmegen, in 2012 and started her bachelor's degree in Psychology at the Universiteit Utrecht. During her bachelor's, she followed the both the Neuropsychology and Clinical Psychology track. This was followed by the Master Clinical Psychology at the Vrije Universiteit Amsterdam. She graduated with distinction (Cum Laude).

She completed her clinical internship in 2017 at the department of 'Early Psychosis' at the Amsterdam University Medical Center. She completed her research internship at GGZ inGeest, working for the Dutch Older Bipolars (DOBi) study, under supervision of dr. Annemiek Dols and dr. Nicole Korten. She published her master thesis in which she investigated the relationship between social and cognitive functioning in older adults with bipolar disorder.

After graduating, she worked as a research assistant and psychologist at GGZ inGeest, and continued working for the Dutch Older Bipolars (DOBi) study. Besides being involved in the DOBi study, she also coordinated the pilot studies 'Braintrain' and 'SPIRIT'. Next to her work as a research assistant, she worked as a psychologist and started the department of Psychodiagnostics together with dr. Sigfried Schouws and Geerke van Sprundel. She started her PhD trajectory in 2019, focusing on recurrence in older adults with bipolar disorder. In September 2019, she started her doctoral training in healthcare psychology at RINO Amsterdam (GZ-opleiding) and GGZ inGeest.

In the spring of 2023, Melis will start her position as a postdoctoral researcher and registered mental health psychologist at the Clinical Psychology section at Leiden University and Leids Universitair Behandel Expertise Centrum (LUBEC).

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