SUBJECTIVE AND OBJECTIVE COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER

SUBJECTIVE AND OBJECTIVE COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER RELATIVE TO SIMILAR NEUROPSYCHOLOGICAL DISORDERS

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Abstract

This thesis presents research investigating objectively and subjectively examined cognitive impairment in Bipolar Disorder (BD) in comparison to disorders with similar cognitive symptomatologies. First, a systematic review and meta-analyses compared the cognitive performance between BD and Mild Cognitive Impairment (MCI) or dementia. Studies included in this review and meta-analyses assessed cognitive performances using multiple objective cognitive assessments. Results from these meta-analyses found greater impairment in BD relative to MCI on motor initiative abilities. Additionally, there were similarities in cognitive deficits on delayed memory recall and visuoconstructional abilities between BD and MCI. For the comparison between BD and dementia, we analyzed the findings of studies comparing BD across different mood states with different types of dementia, where BD in acute mood episode demonstrated greater deficits in attention, working memory, verbal memory, and executive function than behavioral variant frontotemporal dementia (bvFTD). In contrast, overall cognitive functioning and verbal fluency was more impaired in Alzheimer's disease (AD) in comparison to BD during euthymia. Next, we shifted the focus on examining subjective cognitive complaints in BD relative to Major Depressive Disorder (MDD). Our study is unique from previous literature with the same aim considering that it only involved patients recently diagnosed with BD, and subjective complaints were assessed with the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA), an instrument specific to cognitive complaints detected in BD. The findings demonstrate higher subjective cognitive complaints in euthymic BD in comparison to euthymic MDD, suggesting greater self-perceived difficulties in BD, even in

the beginning of the illness. Taken together, findings from the studies presented in this thesis highlight the importance of early detection and intervention of cognitive impairments in BD, with the aim of enhancing cognitive abilities, and prevention of further cognitive degradation with the progression of the disorder.

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List of Abbreviations

AD = Alzheimer's Disease;

ADHD = Attention Deficit Hyperactivity Disorder;

AL = Allostatic Load;

BD = Bipolar Disorder;

BDRS = Blessed Dementia Rating Scale;

BLAD = Battery of Lisbon for the Assessment of Dementia;

bvFTD = behavioral variant Frontotemporal Dementia;

CAMCOG = Cambridge Cognitive Test;

CANMAT = Canadian Network for Mood and Anxiety Treatments;

CBT = Cognitive Behavioural Therapy;

CDR = Clinical Dementia Rating Scale;

CDT = Clock Drawing Test;

COBRA = Cognitive Complaints in Bipolar Disorder Rating Assessment;

CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire;

CRT = Cognitive Remediation Therapy;

DSM = Diagnostic and Statistical Manual of Mental Disorders;

GBD = Global Burden of Disease;

GDS = Geriatric Depression Scale;

HC = Healthy Control;

ISBD = International Society for Bipolar Disorder;

MCI = Mild Cognitive Impairment;

MDD = Major Depressive Disorder;

MDE = Major Depressive Episode

MINI = Mini International Neuropsychiatric Interview;

MMSE = Mini Menta State Examination;

NOQAS = Newcastle-Ottawa Quality Assessment Scale;

ODK = Open Data Kit;

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis;

PTSD = Post Traumatic Stress Disorder;

RAVLT = Rey Auditory Verbal Learning Test;

TMT = Trail Making Test;

UCPel = Universidade Católica de Pelotas;

VFT = Verbal Fluency Test.

Declaration of Academic Achievement

This thesis consists of 4 chapters: Chapter 1 provides an introduction on bipolar disorder and background information on cognitive functioning in bipolar disorder, Chapters 2 and 3 present manuscript of studies currently under review in peer-reviewed journals, and Chapter 4 consists of a general discussion and clinical implications of the findings from Chapters 2 and 3. Dr. Flavio Kapczinski, Dr. Taiane de Azevedo Cardoso, and I were responsible for development of the research questions associated with the studies presented in Chapters 2 and 3.

Concerning the systematic review presented in Chapter 2, I was responsible for assisting in building the search strategy, searching, screening, and extraction of relevant studies, analysis and interpretation of data, and drafting the manuscript for publication. Mr. Aidan McIntyre was also responsible for searching, screening, and extraction of relevant studies. Dr. Taiane de Azevedo Cardoso was in charge of building of the search strategy, literature search, interpretation of data, and drafting the manuscript for publication. Dr. Flavio Kapczinski was involved with the critical editing of the manuscript. The paper from this chapter was submitted to the *Journal of Affective Disorders* in April, 2020.

With regards to the original study in Chapter 3, I was responsible for analysis and interpretation of the data, and drafting of the manuscript. On the other hand, Drs. Karen Jansen, Thaise Campos, Fernanda Moreira, Igor Vieira, Ricardo Da Silva and Luciano Souza were responsible for conception and design of the study, data collection and interpretation, and final edits to the manuscript. Dr. Taiane de Azevedo Cardoso was also involved in data collection and

interpretation, and assisted in drafting the manuscript. Dr. Benicio Frey and Dr. Flavio Kapczinski were involved in data interpretation and critical editing of the manuscript. The paper from this chapter has also been submitted to the *Journal of Affective Disorders* in June, 2020.

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CHAPTER 1

General Introduction

Mood disorders affect more than 300 million people worldwide, which in addition to being one of the most common mental disorders, it also makes them one of the most prevalent global health problems (Judd, 1995; Steel et al., 2014; James et al., 2018). Extensive work reported by the Global Burden of Disease (GBD) implies that mood disorders are among the leading causes of disease burden in the world, associated with increased accident rates, hospitalizations, substance use, and other medical and financial difficulties (Vos et al., 2016; Hall & Wise, 1995). Major depressive disorder (MDD) and bipolar disorder (BD) are the two main mood disorders. Together, MDD and BD are found to have comorbidities with many mental and physical illnesses, including anxiety, substance use disorders, suicidality, as well as asthma, elevated cholesterol, and hypertension (Angst, 1996; Thaipisuttikul et al., 2014; Herrera, 2018). The presence of mood disorders is associated with distressingly large health risks, with every 2 out of 3 suicides occurring in patients with a mood disorder diagnosis (Herrera, 2018).

MDD and BD are particularly characterized by mood fluctuations, affecting the mental, emotional, and physical well-being of a person (Kessing, 2015). Patients with MDD and BD commonly present cognitive dysfunction. Cognitive abilities degenerate throughout the course of BD, accumulating to greater cognitive deficits with the increase in reoccurring mood episodes (Tremain et al., 2020). Dysfunction in specific cognitive domains is often examined

with objective measures, capturing symptoms indicative of abnormalities during acute mood episodes and euthymia. A consistent observation in previous literature is the presence of cognitive deficits in BD (Miskowiak et al., 2018); however, little is known about the *extent* to which various cognition areas are affected. Consequently, there is a rise in interest in subjective perceptions of cognitive deficits with the progression of BD, due to the distinct nature of the disorder. Research investigating cognitive impairment in BD may inform us of (1) the extent to which cognitive areas in BD are affected relative to well-known cognitive disorders, and (2) the subjective experiences of cognitive deficits in BD with the progression of the clinical course of the disorder.

The current work aimed to bring detailed insight on the development of cognitive dysfunction in BD, with the idea of improving our understanding of the progressively degenerating cognitive abilities affected by the repeated occurrence of fluctuating mood episodes. Chapter 1 provides: general background information on BD, a discussion on cognitive functionality in BD during acute mood episodes and euthymia, and a discussion on the importance of differences between subjective perception and objective measurements of cognition. Chapter 2 includes a systematic review and meta-analysis on cognitive impairment in BD relative to other prominent cognitive disorders. This review consists of comparisons from empirical studies in cognitive performance between BD and cognitive disorders such as mild cognitive impairment (MCI) and dementia. Chapter 3 consists of the final manuscript of our cross-sectional study comparing subjective cognitive complaints between BD and MDD through an assessment specifically designed for cognition in BD. Finally, chapter 4 concludes the thesis

with a general discussion of the findings, the strengths and limitations of the current work, and the basis of potential future research ideas.

Bipolar Disorder

Bipolar Disorder (BD) is a very specific mood disorder that affects more than 45 million people worldwide, or approximately 0.6% of world's population (James et al., 2018; Richie & Roser, 2018). The overall lifetime prevalence of bipolar spectrum disorders, as measured across 11 different countries, was found to be 2.6% (Rowland & Marwaha, 2018). However, the prevalence rates of BD vary across different countries due to different cultural factors, familiarity with the disorder, and variations in diagnostic criteria (Rowland & Marwaha, 2018). In Canada, the estimated prevalence rates for BD I and BD II is 0.87% and 0.57%, respectively (McDonald et al., 2015). Currently, the Canadian government regards BD as one of the six most disturbing mental illnesses to the working population, and invests more than $20.7 billion annually to fund healthcare programs addressing these barriers (Stonebridge & Sutherland, 2016).

However, this was not always the case. BD was a relatively unknown concept until the mid-1800s, when a psychiatrist known as Jean-Pierre Falret reported observations of a "circular madness" defined by manic and melancholic episodes (Angst & Sellaro, 2000). Over the next few hundred years, through extensive research and clinical observations, scientists would form a clearer image of the development and the course of BD. Intriguingly, there is no significant difference found in the incidence rates of BD between the periods after recognition of the disorder, and after modernization (recent era) (Atigari et al., 2016). However, more precise

definitions of the symptomatology of BD have led to shorter episodic cycles, possibly due to the development of medical treatments (Angst & Sellaro, 2000; Atigari et al., 2016).

Currently, the diagnostic criteria for BD is established by the Diagnostic and Statistical Manual for Mental Disorders, 5th edition (Angst, 2013). BD is classified as a mood disorder characterized by oscillations of manic/hypomanic and depressive mood states. A manic episode is characterized by the presence of at least 4 of the symptoms of mania, as described in the DSM-5, for at least one week, whereas a hypomanic episode features less severe symptoms, in comparison to a manic episode, lasting at least 4 days (American Psychiatric Association, 2013). In contrast, a depressive state is described by a major depressive episode (MDE) that consists of the presence of 5 or more of the symptoms described in the DSM-5 over a minimum period of 2 consequent weeks (American Psychiatric Association, 2013). The BD spectrum consists of several subtypes of BD, depending on the length and severity of the manic/hypomanic episode. BD I is a subtype of the disorder characterized by the presence of a full manic episode. In contrast, BD II is a subtype of the disorder where the symptoms of an episode are less severe, which is known as a hypomanic episode (American Psychiatric Association, 2013). The symptoms described in the DSM-5 make BD one of the most distinct disorders in the manual.

Estimates of the mean age of onset of BD have a wide range, depending on the presence of risk factors that could trigger the onset. Previous literature suggests that the average age of onset of BD can differ by up to 20 years depending on the presence or complete absence of risk factors (Post et al., 2016). In addition, the difference in mean age of onset between early-onset BD (17.6 years) and late-onset BD (39.2 years) was found to be

approximately 20 years as well (Bellivier et al., 2003). Generally, early-onset BD is considered to begin before the age of 20, and late-onset BD after the age of 40 (Schürhoff et al., 2000; Martino et al., 2013).

A well-known factor for early onset of BD is the presence of the disorder in family relatives (Post et al., 2016; Wilde et al., 2014; Smoller & Finn, 2003; Duffy et al., 2019). Familial risk is considered to be the best predictive factor for the development of BD, with first degree relatives of affected individuals found to have a 10-fold increased risk for the disorder (Smoller & Finn, 2003; Duffy et al., 2019). Several large studies have suggested that the mean age of onset in high-risk people due to presence of family factors is 20 years, with some cases found to start showing symptoms as early as 13 years of age (Wilde et al., 2014; Duffy et al., 2019). Moreover, other clinical and social risk factors may also play a role in triggering the onset of the disorder. Pre-existing clinical diagnoses such as MDD, anxiety, Post-traumatic Stress Disorder (PTSD), and behavioral disorders have often served as precursors to BD (Marangoni et al., 2018; Faedda et al., 2014). These pre-existing disorders may induce the initiation of a manic or hypomanic episode. A widely researched association is the one between childhood trauma and BD. Childhood trauma, such as physical and/or emotional abuse, has been strongly linked to development of BD in later years (Marangoni et al., 2018; de Azambuja Farias et al., 2019; Bortolato et al., 2017). Another social risk factor, which is often associated with childhood trauma, is the abuse of substances such as cocaine, cannabis, and opioids. Young adolescents and adults that frequently consume these substances have been regarded to carry a greater risk of developing BD as well, which may also impact the progression of the disorder (Marangoni et

al., 2018; de Azevedo Cardoso et al., 2020; Strakowski et al., 2017). Consequently, familial, clinical, and social factors can collectively contribute to the predisposition of an individual to BD. In many cases, these risk factors may cause early onset of BD, which is known to cause aggravated clinical outcomes as a result of the disorder (Cardoso et al., 2017; Baldessarini et al., 2012).

BD is often associated and coexists with other psychiatric and/or medical comorbidities, which can be additionally detrimental to the overall health of the person. A broad literature review found a strong association between BD and other psychiatric disorders such as anxiety (71%), substance use disorder (56%), PTSD (39%), and other common Axis I disorders, such as eating disorder and Attention Deficit Hyperactivity Disorder (ADHD) (65%), usually resulting in a more severe course of BD and further complicating the treatment of the disorder (Krishnan, 2005). Moreover, findings from the same study suggest the presence of medical comorbidities in BD at rates higher than predicted by chance, including: migraine (28%), overweight (58%), multiple sclerosis (10%), and type 2 diabetes (10%) (Krishnan, 2005). Understanding the associations between BD and coexisting disorders is difficult due to the uncertainty in the direction of causality between the disorders, which has led to the development of several possible clinical models to explain the co-occurrences (Parker, 2010). Nevertheless, each model comes to a common conclusion that the high rates of comorbidities in BD interfere with the clinical approaches to treatment of BD (Parker, 2010).

Cognitive Functioning in Bipolar Disorder

Close observations of the effects of BD over the years have revealed that cognitive impairment is one of the clinical outcomes resulting from the mood-fluctuating disorder. Cognitive dysfunctionality is now increasingly recognized as a hallmark outcome of BD, persistent across all mood states of the disorder (Goldberg & Roy Chengappa, 2009; Zarate et al., 2000). Although it is hard to calculate the prevalence of cognitive deficits in BD, a study suggested that 64.4% of patients with BD during a depressive episode, and 57.1% of euthymic individuals with BD demonstrate impairments across one or more cognitive domains (Douglas et al., 2018). BD has a heterogeneous course, where affected individuals may experience different types and severities of cognitive and functional symptoms based on various underlying risk factors (Passos et al., 2016; Sparding et al., 2017). Some of the most commonly perturbed cognitive areas in BD studied to date are verbal learning, attention, memory, and executive function (Zubieta et al., 2001; Robinson et al., 2006; Sparding et al., 2017).

Intriguingly, the discrepancy in cognitive abilities between BD and healthy controls is clear across all stages of the disorder, including euthymia, suggesting a significant magnitude of cognitive deficits in BD. Cognitive dysfunction during a manic or depressive episode in BD is evident and expected (Martínez-Arán et al., 2004); however, there is increasing interest in the after-effects of a mood episode on the cognition of a person during euthymia. Besides the disruption of typical cognitive functioning in the presence of manic or depressive symptoms, patients often experience long-lasting deficits in many cognitive areas during remission (Volkert et al., 2016; Torres et al., 2007). A recent systematic review found that executive function,

attention, motor functioning, and working memory (both verbal and visual) have been recognized as the most frequently disrupted cognitive domains in euthymic individuals with BD, as compared to healthy controls (Cullen et al., 2016). The deterioration of functionality and cognitive abilities seen during euthymia signify the extent to which a person may be affected by the disorder (Zubieta et al., 2001; Robinson et al., 2006). It is important to examine the well-being of individuals with BD across different stages to analyze the effects of each mood episode on their overall cognition and functioning.

Previous studies of cognitive dysfunction in BD have noticed changes in the functionality of patients with BD even following their first mood episode, with some studies suggesting that only 1 in 3 patients achieves full functional recovery within a year of their first mood episode (Zarate et al., 2000; Bora & Pantelis, 2015). The presence of cognitive and functional dysfunctionality promptly following the first mood episode is evident across multiple cognitive domains relative to healthy controls (Bora & Pantelis, 2015; Lee et al., 2014; Elshahawi et al., 2010). A single manic episode is sufficient to disturb the cognitive well-being of an individual, with each additional episode further amplifying the impact on their cognitive stability (Elshahawi et al, 2010, MacQueen et al., 2000).

Previous observations suggest that the level of cognitive impairment is positively correlated to the number of mood episodes a person has experienced (MacQueen et al., 2000). The aggregation of the effects experienced by multiple mood episodes can lead to poorer functional and cognitive outcomes (MacQueen et al., 2000), which could partly be explained by the changes in brain structures and increased vulnerability to stress as a result of the

reoccurring episodes (Post, 1993; Cao et al., 2016). Individuals affected with BD usually undergo drastic changes in their behavioral and cognitive responses throughout the course of the disorder.

The progression of clinical outcomes with the occurrence of each additional episode can be explained by the concept of clinical staging and neuroprogression of BD. Within the last 15 years, there has been growing literature on the progressive nature of BD through different stages of the disorder with the increase in recurrent mood episodes (Fries et al., 2012; Rosa et al., 2014; Vieta et al., 2011; Kapczinski et al., 2009). The model proposed by Kapczinski et al. [2009] explains the nature of the disorder through 4 stages, where patients in stage I manage to return to regular functioning levels following their first mood episode, while patients in stage IV have severe functional and cognitive impairments that may make them unable to live independently of others. The different stages of the disorder are based on the number of episodes they have experienced, also taking into consideration the degree of deterioration in functioning, which could be substantial even with a lower number of mood episodes (Kapczinski et al., 2009). Cognitive and overall functioning are seen to be differently affected in different stages of the disorder. Specifically, previous observations have indicated progressive worsening of cognitive abilities throughout the four stages in individuals with BD, where individuals in late stages (III and IV) demonstrated more cognitive impairments than individuals in the early stages (I and II) (Rosa et al., 2014; Cardoso et al., 2015).

Of particular concern are cognitive impairments evident in late stage BD. Cognitive functioning in late stage BD is negatively affected by the accumulation of episodes and chronic

stress over the years of the disorder, known as allostatic load (AL) (Vieta et al., 2013). Features of illness progression such as the increase in number of mood episodes, illness duration, and hospitalization are negatively correlated with cognitive capabilities of the affected individual, leading to poor well-being in later stages of the disorder (Cardoso et al., 2015; Cao et al., 2016).

Bipolar Disorder vs Cognitive Disorders

Noticeable cognitive deficits in BD raise interest about how they relate to other well-known cognitive disorders. Dementia is often the comparand condition to which other psychiatric disorders with cognitive symptoms are measured against. Dementia describes a set of symptoms usually affecting memory, thinking, language, and other higher cortical functions of the brain (Dening & Sandilyan, 2015). Considering that dementia specifically relates to the older population, age-standardized prevalence of dementia in adults above the age of 60 suggest that 5-7% of the world population is affected by some type of dementia (Prince et al., 2013). The most common type of dementia is Alzheimer's disease (AD), responsible for 75% of the cases of dementia worldwide (Dening & Sandilyan, 2015). AD is a progressive type of dementia, causing daily functionality problems centered around episodic memory deficits (Lane et al., 2018). A much less frequently observed type of dementia is behavioural variant frontotemporal dementia (bvFTD), affecting regions in the front of the brain responsible for planning, emotion, motivation and language, causing major behavioral changes by the affected individual (Dening & Sandilyan, 2015). There are certain similarities in cognitive symptoms between the BD and the different types of dementia, which raises the question of whether

there is an association or connection between BD and dementia as the course of BD progresses (Masouy et al., 2011). One of the largest studies looking at BD and dementia found that with each additional mood episode, the rate of admission for dementia among those patients increased by 6% (Kessing & Andersen, 2004). Additional meta-analyses found individuals with BD to be at an increased risk of 2.36 (Diniz et al., 2017) and 2.96 (Velosa et al., 2020) times higher to be diagnosed with dementia in comparison to healthy individuals. Although BD has a heterogeneous course, it is clear that a subset of patients experiencing cognitive symptoms may be linked to even greater cognitive impairments that resemble those of dementia in the later stages of the disorder. However, analyzing the similarity in affected cognitive domains between BD and dementia could carry important information for treatment and prevention approaches to thefurther development of cognitive deficits in BD (Masouy et al., 2011; Diniz et al., 2017).

Mild cognitive impairment (MCI) is another cognitive disorder that has a wide spectrum on the extent to which cognitive domains may be impaired in affected individuals, but typically, MCI is regarded to be less severe than dementia (Sanford, 2017). Similar to BD, individuals with MCI are at risk for potentially developing dementia as the cognitive symptoms worsen over time (Ravaglia et al., 2006; Roberts et al., 2014). Considering the predisposition for both, MCI and BD, to develop dementia-like symptoms with the progression of each disorder, it is interesting to investigate the similarity in affected cognitive domains and the differences in severity between the two disorders. Furthermore, comparisons in cognitive impairments between BD versus MCI, and BD versus dementia, could tell us important information on the extent of severity of cognitive deficits seen in BD relative to different cognitive disorders such

as MCI and dementia. The differences between MCI and dementia could serve as estimates to the range in which cognitive deficits in BD may generally be found in.

Subjective Assessments of Cognition

Evaluating cognitive abilities in BD is crucial, as cognitive performance can be predictive of worse clinical outcomes, such as overall functioning and quality of life (Andreou & Bozikas, 2013; Mackala et al., 2014). Detecting cognitive deficits in the early course of BD is especially important, because it allows for early cognitive intervention strategies to be implemented in the treatment plan for the affected individuals. Earlier cognitive interventions could stimulate individuals to restore or maintain their overall functioning and quality of life more easily, in contrast to later detection of cognitive deficits (Mackala et al., 2014).

Objective cognitive assessments are considered to be a reliable method for evaluation of cognition in BD, with different instruments evaluating different cognitive domains (Sparding et al., 2017). However, subjective cognitive assessments are also valuable for understanding the person's cognitive self-perception, which is found to be correlated with psychosocial difficulties experienced by the person (Demant et al., 2015). The relationship between subjective insight of cognition and objective assessments is complicated, with several studies reporting weak correlations between subjective and objective scores (Svendsen et al., 2012; Martinez-Aran et al., 2005). Despite the discrepancy between different types of assessments, subjectively

experienced difficulties, even when not portrayed by objective assessments, indicate a worse course of the disorder with poor overall functioning in everyday life (Martinez-Aran et al., 2005). In contrast, lack of awareness of cognitive deficits leads to greater self-deception from the reality of their cognitive well-being, which is a barrier to the treatment process and eventually could result in greater cognitive impairments (Pallanti et al., 1999). Cognitive deficits in BD are distinct from other neuropsychological disorders, and may not be captured accurately with general subjective cognitive assessments. Assessments aiming to detect cognitive deficits in BD require specific questions corresponding to the distinct cognitive dysfunctionality of BD, resulting from the distinct nature of mood oscillations in BD. Furthermore, examination for the presence of subjective complaints in the beginning stages of the illness is important for developing appropriate clinical strategies for prevention of unfavourable outcomes of the disorder.

Aim of the Current Thesis

The current thesis sought to investigate the extent and severity of subjective and objective cognitive impairments in BD relative to other disorders with similar symptomatologies. In Chapter 2, the systematic review and meta-analysis comparing cognitive performance in BD in contrast to other cognitive disorders such as MCI and dementia is presented. This study highlights the similarity in affected cognitive domains between the disorders, and provides information on the range of impairment seen in BD relative to MCI and dementia. In Chapter 3, the original manuscript of a cross-sectional study focusing on subjective

complaints in patients recently diagnosed with BD in comparison to MDD. This study investigated the differences in subjective cognitive experiences between the disorders across different phases through the use of Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA), an instrument created precisely for detection of subjective cognitive difficulties in BD. Lastly, Chapter 4 consists of a discussion regarding the findings from Chapters 2 and 3, with a focus on clinical implications of the findings, strengths and limitations of the completed studies, and future directions for relevant research in this field.

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CHAPTER 2

Cognitive impairment in Bipolar Disorder as compared to Mild Cognitive Impairment and Dementia: A systematic review and meta-analysis

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Abstract

Background: To conduct a systematic review and meta-analysis to identify the cognitive abilities in Bipolar Disorder (BD) as compared to Mild Cognitive Impairment (MCI) and dementia.

Methods: We conducted a systematic review and meta-analyses. The literature search was performed with no year and no language restriction. The search yielded 1461 articles, with 1261 remaining after duplicate removal, where 4 studies were suitable for the systematic review and the meta-analyses: 2 for the comparison between BD and MCI, and 2 comparing BD and dementia. Statistical analyses were performed using Rev Man 5.3.

Results: The meta-analyses comparing BD and MCI found that BD presented more cognitive impairment than MCI in motor initiative tasks (SMD: 0.39; 95% CI: 0.16, 0.63, p=0.001), and similar levels of deficit in delayed memory and visuoconstructional abilities. Analyses from our systematic review showed that studies comparing BD and dementia indicated that Alzheimer's disease showed greater cognitive deficits than BD during euthymia, while BD during a mood episode demonstrated higher cognitive impairments than behavioral variant frontotemporal dementia (bvFTD).

Limitations: The small number of studies included.

Conclusion: Our findings could be interpreted in the light of neuroprogression theory, considering that patients with BD presented higher cognitive impairment as compared with MCI. In addition, patients in a current mood episode presented higher cognitive impairment as compared with patients with dementia. However, future studies comparing clinical stages of BD with MCI and dementia are needed to support this hypothesis.

Keywords: Bipolar disorder, mild cognitive impairment, dementia, cognitive impairment, neuroprogression, systematic review, meta-analysis

1. Introduction

Bipolar disorder (BD) is a chronic and recurrent disorder characterized by episodes of mood oscillation[1]. The lifetime prevalence ranges from 0.4% to 2.4% worldwide, varying with the subtype of the disorder[2]. BD affects the overall functioning, and quality of life of the individuals[3,4,5,6]. Additionally, a subset of patients with BD experience neurocognitive impairment[3,7]. Many factors, such as the number of mood episodes, childhood trauma, and severity manic and depressive symptoms, can influence the cognitive performance of the individuals with BD[7]. These deficits are present in several cognitive domains, such as attention, verbal learning, mental flexibility, and memory[8,9].

Although BD presents a heterogeneous clinical course, it is known that a subset of patients manifests a progressive course marked by functional and cognitive impairment[10], and a recent systematic review showed evidences for clinical progression for both unipolar and bipolar disorder, being the progressive trajectory characterized by (i) increased risk of recurrence, (ii) increased duration of episodes, (iii) increased severity of symptoms, and (iv) reduction of the threshold for new episodes[11].This is in line with the neuroprogression theory, which describes that a number of patients with BD present a progressive course characterized by episode acceleration, treatment refractoriness, and functional/neurocognitive impairment[12]. Throughout the course of BD, patients might experience many mood episodes that vary in length of time[13]. Cognitive dysfunction in later stages of the disorder increases with the rise in number and length of mood episodes[12,14]. Prior findings suggest that there are brain changes, such as smaller hippocampal volume in patients with BD than healthy individuals, and greater cognitive

impairment in late stage BD than in early stage BD[14].

Cognitive impairment in late stage BD could raise questions about links to other cognitive disorders. There is a concern regarding the association between BD and dementia due to the cognitive symptoms in some patients[15]. Although the literature looking at associations between BD and dementia is limited, there are reports implying that a previous diagnosis of BD increases the risk of a dementia diagnosis by 2.36 times[15,16]. A recent meta-analysis showed that individuals with BD presented 2.96 times higher risk to develop dementia as compared to controls[17]. These findings suggest that a diagnosis of BD could be a risk factor for dementia. Another intriguing comparison that has not been extensively observed is cognitive performance in BD as compared to mild cognitive impairment (MCI). There have been some similarities noticed between cognitive impairment in BD and MCI[18]. However, to our knowledge, there are no systematic reviews assessing the comparison in cognitive impairment between BD, MCI and dementia. The similarities in the domains of cognitive impairments between these three cohorts raise intriguing questions about the extent to which they differ in cognitive functionality.

Thus, the aim of this study was to conduct a systematic review and meta-analyses to compare the cognitive performance in BD with MCI and/or dementia.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for the present review.

2.1 Search Strategy

A literature search without language or year restriction was conducted on September 4th, 2019, using the following databases: PubMed, PsycINFO, and Embase. We searched for a combination of the following search terms: (Bipolar disorder OR Bipolar Disorders OR Mania OR Bipolar Affective Disorders OR Manic-Depressive Psychosis) AND (Mild cognitive impairment OR Mild cognitive impairments OR Mild Neurocognitive Disorder OR Mild Neurocognitive Disorders OR dementia) AND (cognitive complaints OR neurocognitive performance OR cognitive impairment). The search yielded 1461 articles: (PubMed = 918, PsycINFO = 152, Embase = 391), with 1261 articles remaining after removal of duplicates (Figure 1).

To determine whether an article was relevant to our study, we used the following inclusion criteria: the study should 1) present original data, 2) include patients with BD, 3) and compare them to MCI or dementia, 4) with regards to cognitive complaints/cognitive performance. The exclusion criteria were 1) reviews, 2) meta-analyses and 3) case-reports.

The studies were selected by 2 blind reviewers (MS and AM) who determined if studies met inclusion criteria. Articles were assessed independently by the two raters and disagreements were resolved by consensus in a meeting with a third researcher (TAC). Firstly, the raters

screened articles based on the title and abstract. Then, the researchers screened the selected relevant articles by full text. Duplicates, review articles, and articles that did not fulfill the inclusion criteria were excluded.

2.2 Data Extraction

Two researchers (MS and AM) completed the data extraction process. We extracted the following data: authorship, year of publication, journal, country, aim of the study, population included in the study, study design, assessments, and main results of the study.

2.3 Quality Assessment

Each manuscript included in the review was independently assessed by two blind researchers (MS and AM) using the Newcastle-Ottawa Quality Assessment Scale (NOQAS)[19]. Disagreements were resolved by consensus in a meeting with a third researcher (TAC).

2.4 Statistical Analysis

Random effects meta-analysis was performed using the Rev Man 5.3. We conducted a meta-analysis to assess the differences on common cognitive assessments and its domains of people with BD in comparison to people with MCI. For this purpose, we analyzed the reported means, sample sizes, and standard deviation of common assessments across the two studies comparing BD and MCI. We analyzed scores of tests on motor initiative, delayed memory and visuoconstructional abilities. The reported scores were used to compute the standard mean differences on the tests between the BD and MCI groups. If the information (means and standard deviations) were not reported in the paper, we contacted the authors to request access to the

data. Significance was set as $p<0.05$. Cochrane's Q test was performed to assess for statistical heterogeneity and the Higgins I2 statistic was used to determine the extent of variation between sample estimates with values ranging from 0-100%. For the studies comparing BD and dementia, we could not perform any meta-analyses on commonly assessed cognitive domains and assessments due to the differences in mood states of patients with BD and the different types of dementia across the included studies.

Results

The literature search yielded 1461 articles. Once duplicates were removed, 1261 papers remained. We excluded 1252 studies based on the title/abstract, and another 5 articles based on full-text screening, for a final number of 4 studies to be included in the systematic review. We hand-searched the references of the included studies and found no additional studies to include. Figure 1 displays the selection process for the included papers.

3.1 Characteristics of included studies

Table 1 shows an overview of the included studies. Among the 4 studies included, publication dates ranged from 2009 to 2017. One study was conducted in Brazil, one in The Netherlands, one in Portugal, and one in Israel. Total sample size ranged from 135 (Silva et al. 2009)[18] to 214 (Vijverberg et al. 2017)[20], and mean age ranged from 41 to 71 years.

Two studies compared the cognitive performance between BD and MCI, and two studies assessed cognitive performance between BD and dementia. All 4 studies had a cross-sectional design. Regarding the assessments used for inclusion criteria, all studies used DSM-IV criteria for diagnosis of BD, two studies examined MCI patients through clinical evaluations, two studies used DSM-IV criteria for dementia, and one used different clinical examinations for dementia (Table 1).

3.2 Quality assessments of the included studies

Each study included in this review was examined and critically appraised using the adapted Newcastle- Ottawa assessment scale for cross-sectional studies[19]. Results are shown in Table 2. The maximum score on the scale for cross-sectional studies is 10, and the scores of our included studies ranged from 9 to 10, with a mean score of 9.25. All 4 of the included studies ranked of high quality.

3.3 Cognitive performance between BD and MCI

Two studies assessed the cognitive performance between BD and MCI[18,21], and the main results showed that BD present greater cognitive impairment than MCI, especially in the following specific areas: motor response[18,21], visual selectivity[18,21], conceptual thinking[18], calculation[18], and attention[21]. On the other hand, MCI were significantly more impaired in tests of immediate and delayed recall (logical memory) than people with BD.

Silva et al. (2009)[18] conducted a cross-sectional study including 45 people with BD (mean age 63.8 ± 8.8) and 90 people with MCI (mean age 64.2 ± 8.4). In this study, the Battery of Lisbon for the Assessment of Dementia (BLAD) was used to assess the participants on various cognitive domains such as: attention, motor initiatives, verbal comprehension, verbal and non-verbal abstraction, executive functions, calculation, immediate memory, working memory, learning and verbal memory. The findings showed that the BD group demonstrated more impairment in motor initiative and cancellation task tests, lower cognitive scores in interpretation of proverbs (conceptual thinking), and more calculation errors in comparison to the MCI group. Additionally, the findings suggested significantly higher impairment in tests of immediate and delayed recall (logical memory) in MCI than in BD.

Osher et al, (2011)[21] conducted a cross-sectional study aimed to compare cognitive domains between people with BD and people with MCI. Subjects with BD (n= 51, mean age: 41.3±13.2) had to be euthymic for at least a month prior to the study. Subjects with MCI (n= 162, mean age: 72.8 ± 8.7) were assessed based on a clinical examination independent of the neurocognitive tests of the study. A computerized cognitive assessment battery known as the Global Assessment Battery was used in this study. It comprises of 10 different tests, such as the go-no go task, Stroop interference test, finger tapping, a catch game and simple mathematical calculations, among others. The tests produce scores on 7 different cognitive domains: memory, executive function, visual-spatial processing, verbal function, attention, information processing speed, and motor skills. Subjects with BD and MCI demonstrated approximately equal scores in the memory, executive function, verbal function and information processing speed. The only differences found were between BD and MCI women. Women with BD (n=26) demonstrated

more impairment in visual-spatial processing (p=0.0078), attention (p=0.0066), and motor skills (p=0.0098) as compared to women with MCI (n=92). There were no differences between BD and MCI men in this sample.

3.3.1. Meta-analysis of motor initiative tasks between BD and MCI

Motor initiative tasks from both studies comparing BD and MCI were included in this meta-analysis[18,21]. The two studies made up for a total of 96 subjects with BD, and 252 subjects with MCI. We found significantly worse scores on motor initiative in BD in comparison to MCI, with a significant standard mean difference of 0.39 (95% CI: 0.16, 0.63, p=0.001). Findings from this comparison indicate greater impairment in motor initiative in BD relative to MCI.

3.3.2. Meta-analysis of delayed memory tasks between BD and MCI

Delayed memory recall was also assessed in both of these studies[18,21]. The tasks consisted of recall of words and phrases following a set amount of time after presentation of the items. The findings did not highlight any significant differences in performance on delayed memory recall between subjects with BD and MCI, with a standard mean difference of -0.47 (95% CI: -1.48, 0.53, p< 0.35). This comparison suggests similar magnitude of impairment in delayed memory recall of people with BD and MCI.

3.3.3. Meta-analysis of visuoconstructional abilities between BD and MCI

We also performed a meta-analysis on visuoconstructional abilities between BD and MCI. Results on tasks from both studies were considered for this analysis. Similar to delayed memory tasks, there were no significant differences between MCI and BD in visuoconstructional

performances, with a standard mean difference of 0.20 (95% CI: -0.37, 0.76, p=0.49). The similarity in performances between BD and MCI may suggest similar levels of impairment in visuoconstructional abilities between the groups.

3.4 Cognitive performance between BD and Dementia

We included two studies assessing the cognitive performance between BD and dementia[20,22]. The main results showed that overall cognitive impairment was greater in dementia in comparison to BD, considering the total scores of the screening cognitive tests used in the studies, such as the Cambridge cognitive test (CAMCOG), and the Mini Mental State Exam (MMSE)[20,22]. Additionally, both studies found greater impairment in verbal fluency in dementia in comparison to BD[20,22]. On the other hand, subjects with BD presented greater impairment when compared to subjects with dementia, especially in the following areas: attention, working memory, verbal memory, and executive function[20]. However, it is important to highlight that these findings were reported in a study which included patients with BD in a current mood episode, and cognitive impairment could be associated with the current mood state.

Vijverberg et al (2017)[20] performed a cross-sectional study including 41 non-euthymic BD people (mean age: 71.7 ± 8.8 years), and 173 subjects with bvFTD (mean age: 62.6 ± 8.0 years). The study compared the neuropsychological profiles between the two groups. Out of the 41 BD subjects, 20 were in a manic state and 21 were in a depressive state at the period of assessment. All the analyses were adjusted for age, gender and education level. All neuropsychological data were transformed into z-scores standardized to the performance of the healthy controls in that assessment. To assess cognitive performance in BDs and bvFTDs, the Mini-Mental State

Examination (MMSE) was used. Findings indicated a significantly higher score on the MMSE in BDs (26.7±2.9) than in bvFTDs (24.1±4.5) ($p < 0.001$). The Digit Span Test and the Trail Making Test Part A (TMT A) were used to assess attention, working memory, and mental speed. Subjects with bvFTD had a better performance on the attention and working memory tests than subjects with BD ($p<0.001$). The Rey Auditory Verbal Learning Test (RAVLT) was used for verbal memory comparisons. A significantly better performance was seen in subjects with bvFTD in comparison to BDs ($p<0.001$). To assess for executive function, the Trail Making Test Part B (TMT B) and the Stroop Color-Word Test were used. Findings indicate better performance in people with bvFTD than in people with BD ($p<0.001$). Animal Naming fluency and Letter Naming fluency tests were used to assess verbal fluency. People with BD had a better performance than subjects with bvFTD ($p<0.001$). In summary, the bvFTD group of subjects did significantly better than BD on all of the assessments in this study, with the exception of the animal naming task, where BD demonstrated better verbal and language skills than bvFTD.

Aprahamian et al. (2014)[22] conducted a cross-sectional study including a total sample of 186 people. The sample included people with BD (n=35, mean age 68.6 ± 6.4), and Alzheimer's disease (AD) type dementia without BD (n=30, mean age 74 ± 8.4). Both groups were subjected to the Brazilian version of the Cambridge cognitive test (CAMCOG). The CAMCOG measures performances on orientation, memory, attention, praxis, calculation, abstract thinking and perception. Subjects were also evaluated on scores on the Mini Mental State Exam (MMSE), clock drawing test (CDT), and verbal fluency test (VFT). This study aimed to compare the subdivision groups between BD and non-BD subjects. For the purpose of this systematic review, we performed additional analyses to evaluate the significance in differences in scores between the

groups. The result scores for each test are as follows:

- CAMCOG: BD (94.2 ± 6.3) > Dementia (non-BD) (63.4 ± 11.6) - p<0.001
- VFT: BD (15.9 ± 4.8) > Dementia (non-BD) (10.8 ± 4.7) - p<0.001
- MMSE: BD (27.8 ± 1.7) > Dementia (non-BD) (18.9 ± 3.9) - p<0.001
- CDT: BD (4.2 ± 0.6) > Dementia (non-BD) (2.7 ± 1.0) - p<0.001

The BD group performed significantly better than the AD group on all the assessments in this study, indicating greater cognitive impairment in the AD group in comparison to the BD group.

4. Discussion

These meta-analyses showed that deficits in motor initiative were greater in BD relative to MCI, while the two groups showed similar levels of impairment in delayed memory and visuoconstructional abilities. Additionally, our systematic review showed that patients with BD in a current episode demonstrated higher cognitive impairments than people with bvFTD, especially on the following areas: attention, working memory, verbal memory, and executive function. In contrast, we found greater deficits on overall cognitive tests and verbal fluency in dementia in comparison to BD.

4.1 Comparison between BD and MCI

We performed a meta-analysis on cognitive domains commonly observed across the studies comparing BD and MCI. We found a significant difference in motor initiative tasks across the 2 studies[18,21], where BD displayed greater impairment relative to MCI. Psychomotor

dysfunctionality in BD has been observed in previous studies[23,24], and it is a cognitive domain included in many diagnostic assessments. An intriguing suggestion from our meta-analysis is that psychomotor tasks, such as motor initiative, may be impaired to a greater extent in BD relative to MCI. In addition to familiar findings about motor deficits in comparison to healthy population, this may bring a better understanding of the magnitude of dysfunctionality relative to cognitive disorders.

Furthermore, we compared the two groups on performance in delayed memory tasks in both studies. Memory is a broad cognitive concept that has been studied for hundreds of years. Different components of memory have been of focus when studying BD. Specifically looking at delayed memory recall, previous studies have found significant impairments in BD, especially during a manic episode, relative to unipolar depression and healthy individuals[25,26]. Moreover, results from our meta-analysis may suggest similar levels of impairment in delayed recall in BD and MCI. Across the 2 studies included, the differences between the two groups were not statistically significant[18,21]. Surprisingly, this may indicate that previously evident memory deficits in BD may be as far-reaching as deficits seen in MCI.

Visuoconstructional abilities were another common interest for the 2 studies comparing BD and MCI. These tasks evaluated the subjects' ability to process visual information and replicate it (by drawing it) without the initial stimulus. The limited literature on visuoconstructional abilities in BD are indicative of deficits on similar tasks in euthymic BD in comparison to healthy controls[27,28]. There were no significant differences between BD and MCI on these tasks in the two studies from our meta-analysis, once again suggesting similar cognitive

impairments between BD and MCI. Deficits in visuoconstructional skills in BD are an interesting concept that should be investigated further for a better understanding of the underlying components.

Altogether, these data could be interpreted in the light of neuroprogression theory. BD showed greater cognitive impairment in a motor initiative task, and BD was as impaired as MCI in delayed memory recall and visuoconstructional abilities.

4.2 Comparison between BD and dementia

As expected, we also found that older adults with dementia demonstrated significantly greater cognitive deficits than in BD during euthymia on cognitive assessments such as the CAMCOG, MMSE, verbal fluency and clock drawing[22]. These batteries imply that cognitive domains, such as attention, memory, perception, and orientation, are less impaired in BD during euthymia relative to dementia. However, in the study by Vivjerberg et al., subjects with BD who were currently experiencing either a manic or depressive episode demonstrated greater impairments in attention, memory, learning, and executive function, compared to the group of people with dementia[20]. It is interesting to notice the difference in cognitive performances in BD during a mood episode and euthymia, relative to cognition in dementia.

The differences in cognitive performance in BD during euthymia and an acute mood episode have previously been observed in several studies[29,30]. People with BD who are currently in a manic or depressive episode display higher cognitive impairments than euthymic people with BD, particularly in cognitive areas such as verbal learning, memory, verbal fluency, and executive

function[29,30]. Furthermore, current findings from this review scale the differences in cognitive deficits across different mood stages in BD relative to deficits in dementia. Analysis of the findings from both studies comparing BD and dementia in this review indicate that cognitive impairments in BD during a mood episode may not only be greater than BD during euthymia, but also greater than cognitive impairments seen in dementia[20]. However, cognition in BD during euthymia is not affected to the extent of deficits seen in dementia[22], reinforcing significant variability in cognitive abilities across different mood stages in BD.

4.3 Limitations

The findings in this review and meta-analyses should be interpreted considering some limitations. Our major limitation was the small number of studies included in this review. Due to the specificity of the inclusion criteria, the number of studies satisfying the criteria was limited. Also, the studies included in this systematic review were conducted in a small sample size. In addition, the studies included were heterogeneous regarding the sample selection. Of note, 3 of the 4 studies included euthymic BD patients[18,21,22], and 1 study included patients during a mood episode[20]. This could potentially bias the results we observed regarding the cognitive performances of subjects with BD, due to the differences in cognitive stability during different mood states of BD. Lastly, 1 of the studies comparing BD and dementia included individuals with bvFTD, while the other study consisted of subjects with AD. Despite these limitations, this is the first systematic review and meta-analysis comparing the cognitive performance in BD, MCI and dementia, and the studies included were regarded to be of high quality as per the NOQAS quality of assessment tool.

5. Conclusion

To our knowledge, this is the first systematic review and meta-analyses comparing the cognitive abilities of BD in comparison to MCI and dementia. The findings in this systematic review and meta-analyses are in line with the theory of neuroprogression. The cognitive testing of people with BD in comparison to people with MCI could imply that the progression of BD leads to the development of cognitive deficits even greater than those of other cognitive disorders. The clinical outcomes of the progression of BD are evident through the cognitive decline throughout the course of the disorder[31]. However, the studies included in this systematic review and meta-analyses did not separate the subjects with BD according to their clinical stages. Differences in cognitive abilities between early and late-stage BD highlight the progression of clinical symptoms in BD. Patients in later stages of BD typically demonstrate greater cognitive deficits than early-stage patients due to the progression of the disorder[5,32,33]. Presumably, cognition in late-stage BD might be more similar to cognition in MCI or dementia, in comparison to early-stage BD.

In conclusion, more studies are needed to clearly observe the differences in cognition between BD, MCI and dementia. Future studies should analyze the cognition of people with BD according to their clinical stage (early vs late-stage) in comparison to other cognitive disorders, such as MCI and dementia. The distinction by clinical stages of BD would highlight the progression of clinical outcomes of the disorder, indicating the progression of cognitive symptoms towards those of other cognitive disorders. Future investigations should also focus on proper categorization of subjects based on their current mood state and subtype of diagnosis, as there

may be differences in cognitive functionality across different mood states and subtypes. Nevertheless, deficits in cognitive domains such as attention, motor initiative, visual perception and executive function of people with BD are evident. The clinical outcomes of the disorder could result in detrimental effects on the cognitive functioning of people with BD, resulting in cognitive deficits similar to those of MCI and dementia.

Tables

Table 2.1: Characteristics of all the included studies.

Author (year), Journal, Country	Aim	Population	Study design	Assessments	Main results
Vijverberg, et al. (2017), J Clin Psychiatry, Netherlands	Compare neuropsychological profiles in bvFTD with MDD, BD, and schizophrenia, in older patients with active symptoms.	MDD = 42 Non-euthymic BD= 41 Non-remitted schizophrenia= 47 Probable/definite bvFTD= 173 Healthy controls= 78	Cross sectional	- MMSE - Digital span test - TMT A & B - RAVLT - Stroop Test -Naming Fluency Test	Executive function: bvFTD>** BD Attention & working memory: bvFTD>** BD Verbal memory: bvFTD>**BD Verbal fluency: BD>** bvFTD Cognitive performance: Bd>** bvFTD
Aprahamian, et al. (2014), Am J Geriatr Psychiatry, Brazil	Investigate the performance on cognitive screening tests in a sample of older adults with BD, as compared to non-BD subjects.	N= 186 (BD=86, Non-BD=100) AD= 56 (26 with BD) Cognitively unimpaired= 65 (35 with BD)	Cross sectional	- CAMCOG - VFT - MMSE - CDT	CAMCOG: BD>** Dementia VFT: BD>* Dementia MMSE: BD>** Dementia CDT: BD>** Dementia
Osher, et al. (2011), Psychotherapy and Psychosomatics, Israel	Compare neuropsychological functioning of euthymic BD patients vs MCI patients and healthy controls.	BD I = 51 MCI= 162 Healthy= 495	Cross sectional	- Global Assessment Battery	Women MCI> Women BD in visual-spatial processing, attention, & motor skills
Silva et al. (2009), Int J Geriatr Psychiatry, Portugal	Characterize cognitive deficits of patients with BD in comparison to MCI	N=135 BD= 45 MCI= 90	Cross sectional	- BLAD - MMSE - CDR - BDRS - GDS	MCI> BD in Attention, motor initiative, verbal abstraction & calculation tasks BD>MCI in episodic memory tasks

Legend: The sign ">" represents a better score on the assessments, indicating less impairments. * = <0.05, ** = <0.01; BD= Bipolar Disorder; MDD = Major Depressive Disorder; MCI = Mild Cognitive Impairment; bvFTD = behavioral variant Frontotemporal Dementia; AD = Alzheimer's Disease; MMSE = Mini Mental State Examination; TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test; CAMCOG = Cambridge Cognitive Test; CDT = Clock Drawing Test; VFT = Verbal Fluency Test; BLAD = Battery of Lisbon for the Assessment of Dementia; CDR = Clinical Dementia Rating Scale; BDRS = Blessed Dementia Rating Scale; GDS = Geriatric Depression Scale;

Table 2.2: Quality assessment of the included studies using the Newcastle-Ottawa Quality Assessment Scale.

Author (year)	Representativeness of the sample (Selection bias)	Sample size (Selection bias)	Non-respondents (Selection bias)	Ascertainment of exposure (Selection bias)	Comparability (Comparability bias)	Assessment of outcome (Outcome bias)	Statistical test (Outcome bias)	Total score
Vijverberg et al. (2017)	1	-	1	2	2	2	1	9/10
Aprahamian et al. (2014)	1	-	1	2	2	2	1	9/10
Osher (2011)	1	-	1	2	2	2	1	9/10
Silva et al. (2009)	1	1	1	2	2	2	1	10/10

Figures

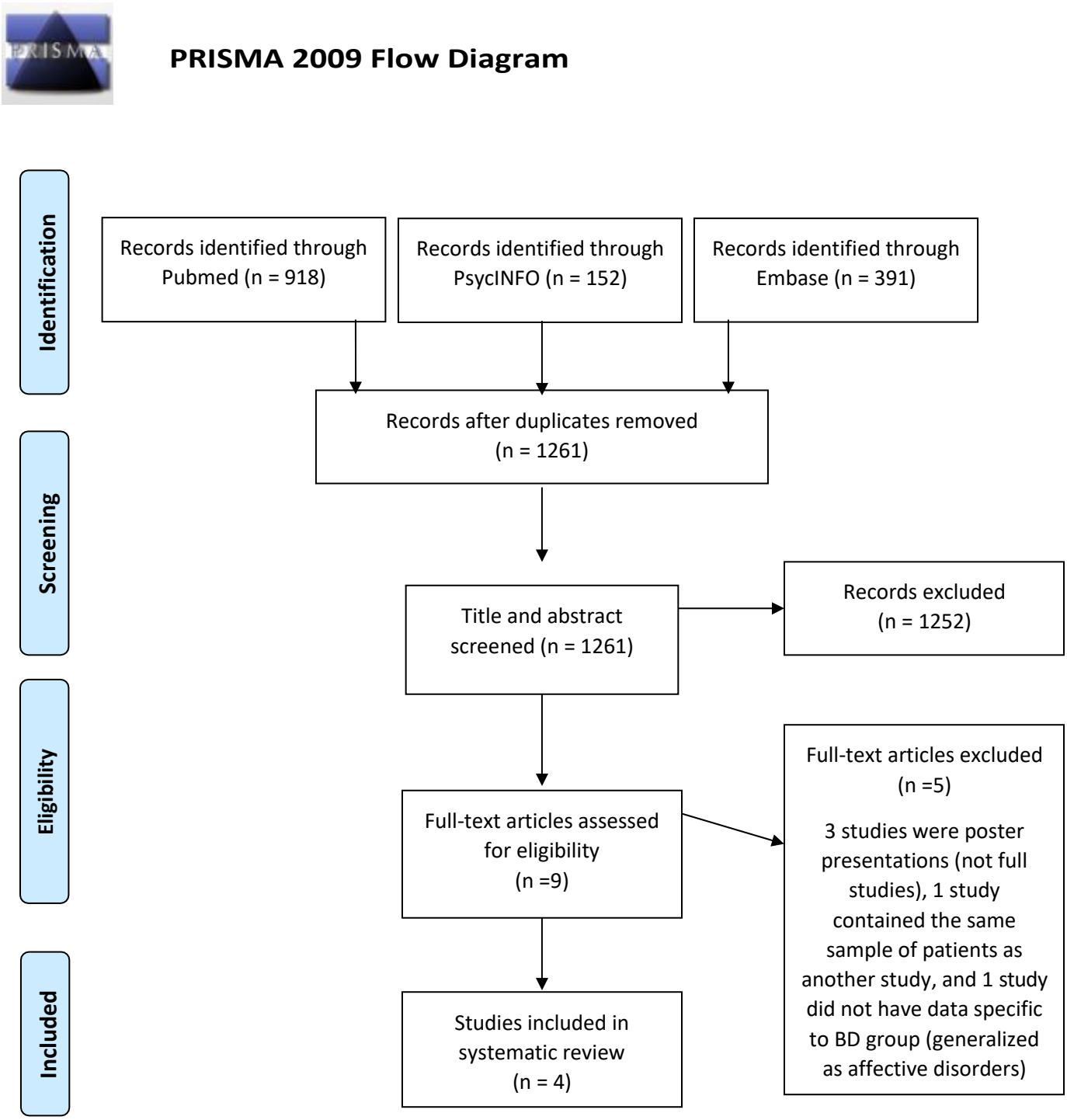

Figure 2.1: PRISMA flow diagram of the selection process for the inclusion of studies for this systematic review.

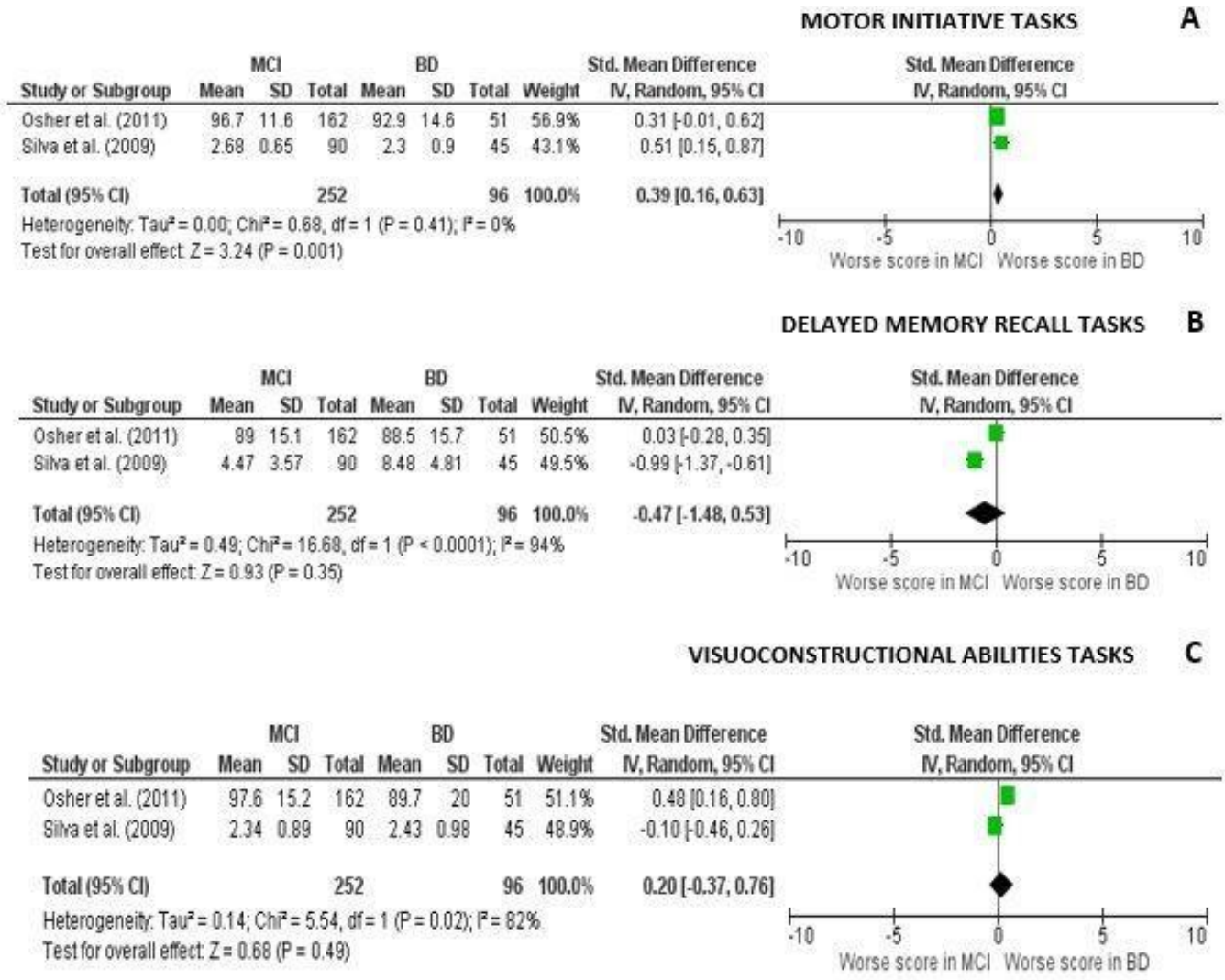

Figure 2.2: Forest plot of scores of the meta-analyses comparing between bipolar disorder (BD) and mild cognitive impairment (MCI); **A)** shows the comparison between the two groups on motor initiative tasks; **B)** shows the comparison between the groups on delayed memory recall tasks; **C)** shows the comparison on visuoconstructional abilities tasks.

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CHAPTER 3

Cognitive complaints in individuals recently diagnosed with bipolar disorder: a cross-sectional study

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Abstract

Aim: To assess the differences in subjective cognitive dysfunction between major depressive disorder (MDD) and recently diagnosed bipolar disorder (BD) across euthymia and mood episodes.

Methods: This is a cross-sectional study corresponding to the second wave of a longitudinal study. The first wave consisted of subjects aged between 18 and 60 diagnosed with MDD. In the follow up after three years (second wave), conversion from MDD to BD diagnosis was assessed by qualified psychologists using the Mini International Neuropsychiatric Interview (MINI-Plus). Subjects were categorized in four diagnostic groups: euthymic MDD, MDD in a current mood episode, euthymic BD, and BD in a current mood episode. All subjects completed the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA), an instrument specifically designed for detecting subjective cognitive deficits in BD.

Results: The total sample (n=468) included 410 subjects with MDD and 58 individuals recently diagnosed with BD. We subdivided the 2 groups based on their current mood state, and found a significant difference in COBRA total scores between euthymic BD individuals (median 17.00 [IQR: 8.75 - 20.75]) and euthymic MDD subjects (median 8.00 [IRQ: 5.00 - 14.00], p=0.002), showing higher subjective cognitive dysfunction in individuals recently diagnosed with BD, during euthymia. The differences remained significant after adjusting for the presence of lifetime psychotic symptoms. We found no differences between MDD and BD, when they were in a current mood episode.

Limitation: The small sample size of individuals with BD.

Conclusion: The findings suggest a higher presence of subjective cognitive complaints among individuals recently diagnosed with BD in comparison to individuals with MDD, during euthymia.

Keywords: Cognitive complaints, Bipolar Disorder, Major Depressive Disorder, Mood Disorders.

1. Introduction

Bipolar disorder (BD) is a severe psychiatric disorder, with prevalence rates ranging from 0.5 to 5% worldwide (Clemente et al., 2015; Rowland & Marwaha, 2018). A hallmark symptom frequently observed with the onset of BD is cognitive dysfunction (Elias et al., 2017; Schouws et al., 2009), with previous studies suggesting that up to 57% of euthymic patients demonstrating impairments in more than one cognitive domain (Douglas et al., 2018). Cognitive deficits in BD during a manic or depressive episode are expected and evident (Cardoso et al., 2015); however, cognition is also deteriorated during euthymia in patients with BD (Zubieta et al., 2001). Some of the most commonly affected cognitive domains throughout the course of BD include attention, processing speed, and memory (Latalova et al., 2011; Van Rheenen et al., 2020). The wide range of mood oscillations in BD may lead to noticeable cognitive deficits even at the early stages of the disorder (Szmulewicz et al., 2018).

In most cases, the onset of BD is preceded by a diagnosis of major depressive disorder (MDD) (Dudek et al., 2013). Clinical and environmental factors, such as treatment-resistance to antidepressants, psychotic features and substance abuse among others, are predictive factors for the conversion from MDD to BD (Dudek et al., 2013; de Azevedo Cardoso et al., 2020). Although cognitive impairment is evident in both BD and MDD, differences in the progressive courses of the disorders lead to distinctive levels of cognitive deficits in each disorder (MacQueen & Memedovich, 2017; Bo et al., 2019; Taylor Tavares et al., 2007). The progression of BD leads to more severe cognitive deficits than those seen in MDD, which is evident in cognitive areas such as delayed memory, executive function, and visuomotor abilities (Gildengers et al., 2012).

Depending on the severity and stage of the disorder, cognitive deficits can have different outcomes between these mood disorders. Examination of cognitive capacity in mood disorders is additionally important as it is a predictive factor of poor quality of life, unemployment, and overall worse functioning in affected individuals (Cotrena et al., 2016; Tse et al., 2014). By early tracking and treating of the detected cognitive deficits, the chances of more favorable outcomes are increased.

Objective cognitive assessments are frequently used for cognitive evaluations. However, subjective cognitive complaints coming from the affected individual's perspective are also important for understanding the complete picture of their psychological and cognitive well-being. The relationship between objective and subjective cognitive measurements is notoriously controversial and inconsistent, with many studies finding weak correlations between the two (Demant et al., 2014; Srisurapanont et al., 2017; Svendsen et al., 2012). Clinicians frequently depend on reliable objective assessments to evaluate the patients' cognitive stability. However, insight on subjective cognitive complaints may help clinicians better understand the patient and the treatment approach required. Findings from a study focusing on the self-perception of patients with BD of their cognitive abilities suggest that patients who were more aware of their cognitive deficits had a better sense of the clinical outcomes from the progression of their disorder (Martínez-Arán et al., 2005).

The limited number of studies comparing subjective cognitive complaints between BD and MDD have not found any significant differences between the groups (Miskowiak et al., 2012; Svendsen et al., 2012). These studies, however, only included euthymic MDD and BD patients with a mean of 8 to 10 years duration of the illness (Miskowiak et al., 2012; Svendsen et al., 2012).

To the best of our knowledge, subjective cognitive complaints in people recently diagnosed with BD in comparison to MDD, taking into consideration their current mood status, has not been studied. In addition, subjective cognitive instruments specifically designed for cognition in BD, could be very helpful in improving our understanding of cognitive impairments in BD. The present study evaluated subjective complaints using an instrument tool that is recommended by the International Society for Bipolar Disorders (ISBD) cognition task force, known as the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) (Miskowiak et al., 2018). The COBRA is a newly validated subjective cognitive assessment, specifically designed for detecting cognitive complaints among individuals with BD (Rosa et al., 2013).

Thus, the aim of this study was to assess the differences in subjective cognitive complaints between MDD and individuals recently diagnosed with BD across different mood stages (euthymic or during a mood episode) with the use of COBRA.

2. Methods

2.1 Study design and participants

This is a cross-sectional study corresponding to a second wave of a cohort study including an outpatient sample of individuals diagnosed with MDD at baseline. The full description of the cohort study has been previously published (Pedrotti Moreira et al., 2019; de Azevedo Cardoso et al., 2020). Briefly, the first wave included 585 participants diagnosed with MDD from 18 to 60 years old. The first phase was carried out at the Research and Extension in Mental Health Clinic of the Universidade Católica de Pelotas (UCPel) between 2012 and 2015. All subjects diagnosed

with MDD assessed in the first phase were invited to participate in the second phase. The second phase took place between 2017 and 2018, averaging 3 years after the first wave. All participants agreed to participate in the study by providing their free and informed consent. This study was approved by the Research Ethics Committee of the UCPel under protocol number 502.604.

2.2 Assessments

Psychiatric diagnosis: The diagnosis of mood disorders was performed by trained psychologists using the Mini International Neuropsychiatric Interview Plus at both waves. For the purpose of the present study, we divided the total sample into four groups, according to the MINI-Plus: MDD currently euthymic, MDD in a current episode, recently diagnosed BD currently euthymic, and recently diagnosed BD in a current mood episode (depressive or (hypo)manic episode). Considering that patients received a BD diagnosis within the last three years, we defined it as recently diagnosed BD in this sample. Importantly, weekly meetings were conducted to discuss cases; in cases where the interviewer had any doubt concerning the BD diagnosis, a psychiatrist was invited to evaluate the case. The MINI-Plus was also used to assess the suicide risk.

Sociodemographic and clinical information: All subjects answered a questionnaire collecting sociodemographic data, which included: age, sex, and years of education, as well as clinical characteristics such as psychotic symptoms and self-reported current types of medications used. Psychotic symptoms were considered as present if the participant answered "Yes" to any of the following questions: (1) "Did you ever believe that someone was spying on you or was conspiring against you or trying to harm you?"; (2) "Have you ever heard things that

other people could not hear, such as voices?"; and (3) "Have you ever seen anything or someone that other people present could not see, that is, did you have visions when you were fully awake?".

Cognitive complaints: Subjects also completed the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA), a self-report instrument developed for detecting subjective cognitive complaints experienced by bipolar patients (Rosa et al., 2013). The COBRA consists of 16 items, which measure subjective cognitive dysfunctions, including executive function, processing speed, working memory, verbal learning and memory, attention/concentration, and mental tracking. All items are rated using a 4-point frequency scale, where 0 = never, 1 = sometimes, 2 = often, and 3 = always. The COBRA total score is obtained by summation of the scores of each item. Higher scores represent more subjective cognitive complaints. The instrument was validated for the Brazilian population, and we used this version in the current study (Lima et al., 2018).

2.3 Statistical Analysis

The data were collected directly in tablets using the Open Data Kit (ODK) platform. After, the data were transferred to the SPSS where the statistical analyses were performed. To describe the sample characteristics among the two groups (euthymic BD vs euthymic MDD or BD in a current mood episode vs MDD in a current episode), we performed chi-square and student t tests. To analyze these two groups on the total COBRA scores, we performed a Mann-Whitney U test. We used a non-parametric test for the bivariate analysis because the distribution of the outcome (COBRA scores) was asymmetric. We created a box plot graph using the Prisma

GraphPad. Finally, we performed a linear regression to adjust the analysis for potential confounder factors. Before performing the linear regression, we transformed the COBRA total score through a square root transformation, in order to have a symmetric distribution. As potential confounding factors, we considered the variables associated to both the dependent variable (COBRA scores - square root transformed), and the independent variable (euthymic MDD vs euthymic BD), with $p<0.20$. A final model was reached using a manual stepwise removal of each non-statistically significant variable. Furthermore, significance was set at $p<0.05$.

3. Results

The final sample of this study consisted of 468 subjects. We divided the sample in 4 groups, based on their diagnosis and current mood state. Out of the 468 participants, 261 were euthymic MDDs, 149 were MDDs currently depressed, 16 were euthymic BDs, and 42 were BDs currently in a (hypo)manic or depressive episode. The comparisons analyzed were based on the diagnosis and current mood state as well, leading to 2 different comparisons: euthymic MDD vs euthymic BD, and MDD in a current mood episode vs BD in a current mood episode. The sociodemographic characteristics of the sample per group are described in table 1. There was a significant difference in age between MDD and BD in current mood episodes ($p=0.036$), where the MDD group was older than the BD group.

Table 2 shows the comparisons between groups on several clinical variables. The only significant differences found was between the euthymic individuals, where BDs (50.0%) indicated a significantly higher presence of psychotic symptoms than MDDs (24.3%, $p=0.023$). In addition,

we gathered information on the current medications used by participants across the groups. There were no differences between the euthymic or between the individuals currently in a mood episode in the use of mood stabilizers, antipsychotics, benzodiazepines, or antidepressants.

The medians and interquartile ranges on COBRA scores for the mood disorders groups were as follows: 8.00 (5.00-14.00) for euthymic MDD, 17.00 (8.75-20.75) for euthymic BD, 21.00 (13.00-30.00) for MDD in a current mood episode, and 21.50 (10.00-29.50) for BD in a current mood episode. We found a significant difference between euthymic MDD and euthymic BD subjects (p=0.002), while no differences were found for the comparison between MDD currently depressed and BD in a current mood episode (p=0.739) (Figure 1).

Finally, we performed a linear regression to adjust the analysis for potential confounders. In this model, we included individuals with euthymic MDD and euthymic BD, and found that the differences on COBRA scores remained significant (B=0.85; CI 95%: 0.22-1.48; R^2=0.099; p=0.008) after adjusting for the presence of lifetime psychotic symptoms. Due to missing data on COBRA scores, we analyzed 267 observations out of a total of 277 subjects included in these two groups.

4. Discussion

This study showed that individuals recently diagnosed with BD during euthymia presented higher levels of cognitive complaints as compared to individuals diagnosed with MDD during euthymia.

Results from this study are in line with previous findings suggesting the presence of cognitive impairment in BD, which has become a well-established feature of the disorder (Robinson & Ferrier, 2006; Goldberg & Chengappa, 2009, Van Rheenen et al. 2020). More specifically, our findings converge with the limited literature on subjective complaints in people with BD, which are extremely important for their overall functioning (Van Rheenen & Rossell, 2014; Demant et al., 2015).

Contrary to previous observations, this study found higher levels of cognitive complaints in recently diagnosed BD patients relative to MDD patients, both during euthymia. Two prior studies comparing BD and MDD did not find any notable differences in cognitive complaints between the groups (Svendsen et al., 2012; Miskowiak et al., 2012). However, both of these studies set a loose inclusion criteria to euthymic patients aged 18-65, without focusing on the duration of the patient's disorder too much. In contrast, in the present study we observed the effects of the disorder on subjective perception of cognitive abilities in recently diagnosed individuals with BD (within the past 3 years). In addition, another major difference is the use of the COBRA in the present study, which is specifically designed for BD, in comparison to the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), a

general cognition questionnaire used in previous studies. The CPFQ is a 7-item self-report questionnaire consisting of questions regarding the general cognitive well-being of patients with any mood disorders, anxiety, and other neuropsychiatric conditions associated with cognitive impairments (Fava et al., 2009). In contrast, the 16-item instrument used in this study was specifically designed for common cognitive complaints found in patients with BD, accurately depicting the presence and distinction of cognitive symptoms in BD, relative to other neuropsychiatric conditions (Rosa et al., 2013).

The notable comparison from our results is that between euthymic BD and euthymic MDD subjects, where subjects who were currently stable still reported experiencing cognitive difficulties. Of note, previous findings indicate the importance of assessing cognition in patients with BD during euthymia, demonstrating the aftereffects of a manic-depressive episode on a person's cognition (Volkert et al., 2016; Sadana et al., 2019). We did not see any differences in COBRA scores between BD and MDD patients in a mood episode, which is in line with previous literature comparing cognitive abilities during acute mood episodes between the two mood disorders (Godard et al., 2011).

In fact, the indications of cognitive deficits reported by patients with BD in our study converge with previous findings of objectively assessed cognitive deficits in patients recently diagnosed with BD (Bora & Pantelis, 2015; Elshahawi et al., 2011). However, to the best of our knowledge, this is the first study assessing subjective cognitive complaints among patients recently diagnosed with BD.

4.1 Limitations and advantages

The main limitations of our study are the small sample size of BD patients, especially in the euthymic subgroup. In addition, another limitation could be the missing clinical information of patients, such as the number of episodes experienced to date, which could consequently have an impact on the cognitive stability of patients. Another possible limitation is the wide range in age of participants included in our study (18-60 years old). Despite the recent diagnosis with BD, the average age of the participants in our sample is greater than the typical onset of BD, which occurs in late adolescence to early adulthood (Joyce, 1984). Lastly, the cross-sectional design of this study limits our ability to attribute causality between the variables, considering the cognitive complaints were measured at a single time point. In contrast, a great advantage of our study is the inclusion of patients recently diagnosed with BD for the assessment of subjective cognitive complaints, which has not been assessed before. Moreover, we used a newly validated subjective cognitive assessment tool (COBRA), specifically designed for detecting complaints in BD, allowing for a more accurate representation of subjective cognitive well-being of the subjects.

4.2 Conclusion

In conclusion, our study found significant differences in subjective cognitive complaints between BD and MDD during euthymia. Findings from this study could be of great significance to further improving our clinical approach to cognitive impairments in BD. The heterogeneity of cognitive impairments in BD should continuously be monitored for effective clinical approaches to BD, considering the variation in efficacy of treatments for different BD subgroups (Tsapekos et

al., 2020). A patient's self-perception of their cognitive disability can be indicative of the progression of the disorder and the extent to which different cognitive domains are affected by it. Future investigations should focus on evaluating a greater sample size of patients with BD, and consider more clinical variables that could be interfering with the cognition of individuals diagnosed with BD.

Tables

Table 3.1: Sociodemographic characteristics across the groups.

Variables	Euthymic MDD (n=261)	Euthymic BD (n=16)	p-value	MDD in a current mood episode (n=149)	BD in a current mood episode (n=42)	p-value
Sex			0.122			0.301
Female	213 (81.6%)	16 (100%)		127 (85.2%)	39 (92.9%)	
Male	48 (18.4%)	0		22 (14.8%)	3 (7.1%)	
Age	40.69 (±11.48)	38.69 (±11.38)	0.500	41.00 (±11.22)	36.90 (±10.57)	0.036
Years of Education**	11.72 (±4.25)	10.50 (±4.79)	0.270	10.29 (±3.72)	10.40 (±5.42)	0.897

**Variable contains missing data for 2 subjects in the Euthymic MDD group.

Table 3.2: Clinical characteristics across groups.

Variables	Euthymic MDD (n=261)	Euthymic BD (n=16)	p-value	MDD in a current mood episode (n=149)	BD in a current mood episode (n=42)	p-value
Suicide Risk*			0.391			0.704
No	202 (78.0%)	11 (68.8%)		59 (39.6%)	18 (42.9%)	
Yes	57 (22.0%)	5 (31.3%)		90 (60.4%)	24 (57.1%)	
Lifetime Psychotic Symptoms*			0.023			0.727
No	196 (75.7%)	8 (50.0%)		75 (50.7%)	20 (47.6%)	
Yes	63 (24.3%)	8 (50.0%)		73 (49.3%)	22 (52.4%)	
Current Medications						
Mood Stabilizer*			0.964			0.110
No	246 (96.9%)	13 (92.9%)		141 (97.2%)	35 (89.7%)	
Yes	8 (3.1%)	1 (7.1%)		4 (2.8%)	4 (10.3%)	
Antipsychotics*			1.000			0.441
No	248 (96.1%)	14 (93.3%)		133 (92.4%)	38 (97.4%)	
Yes	10 (3.9%)	1 (6.7%)		11 (7.6%)	1 (2.6%)	
Antidepressants*			0.658			0.315
No	172 (73.2%)	10 (83.3%)		82 (66.1%)	27 (75.0%)	
Yes	63 (26.8%)	2 (16.7%)		42 (33.9%)	9 (25.0%)	
Benzodiazepines*			1.000			0.168
No	191 (80.3%)	9 (81.8%)		81 (64.8%)	27 (77.1%)	
Yes	47 (19.7%)	2 (18.2%)		44 (35.2%)	8 (22.9%)	

* Variables contain missing data.

Figures

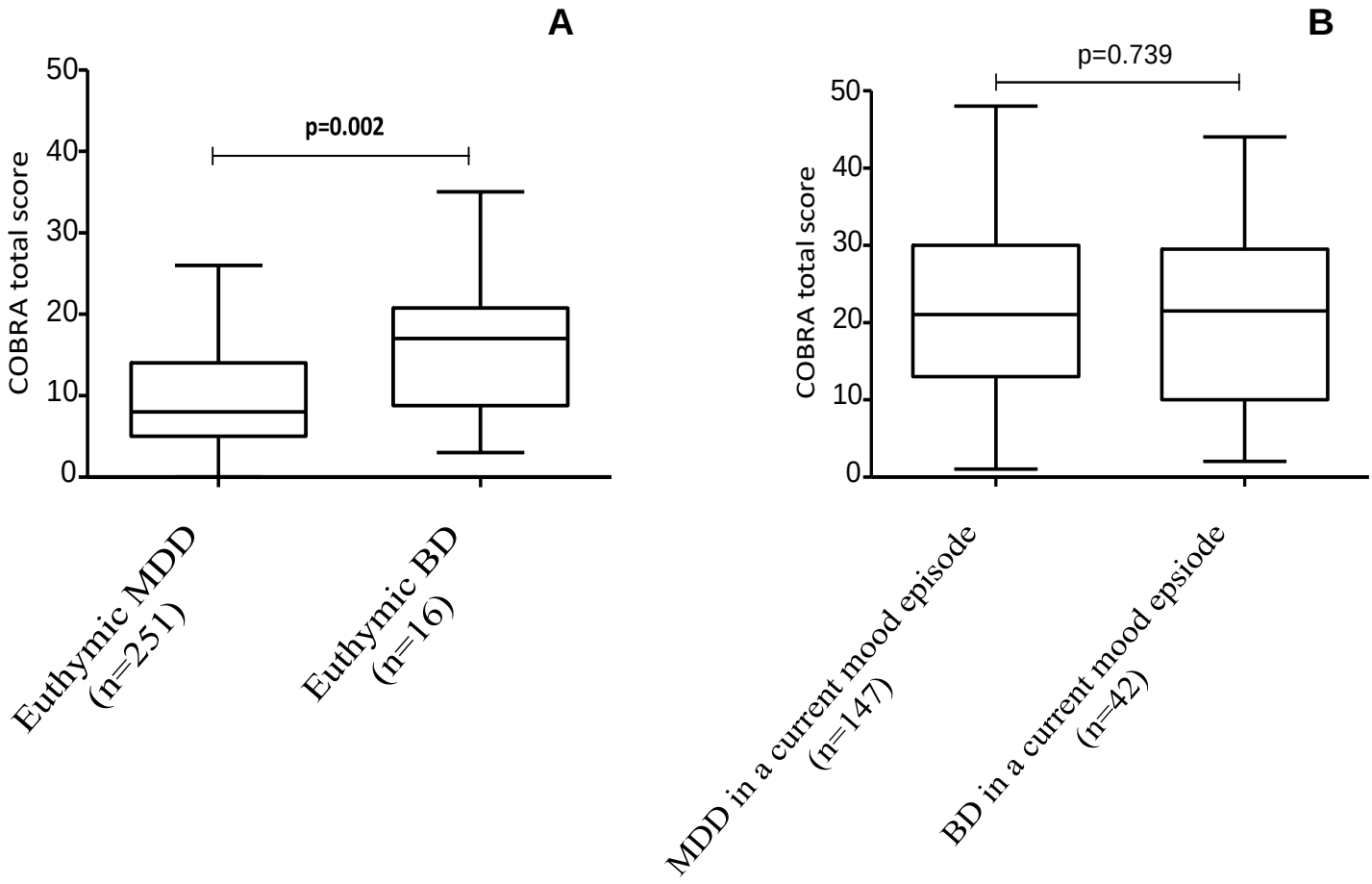

Figure 3.1: Cognitive complaints across diagnosis groups

Legend: COBRA: Cognitive Complaints in Bipolar Disorder Rating Assessment**;** MDD: Major Depressive Disorder; BD: Bipolar Disorder.

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CHAPTER 4

General Discussion

The current thesis aimed to examine cognitive impairments in Bipolar Disorder (BD) as indicated through both subjective and objective assessments. A systematic review and meta-analysis on cognitive deficits in BD relative to Mild Cognitive Impairment (MCI) and dementia, presented in Chapter 2, provided us with an understanding of the extent to which different cognitive domains in BD are impaired in comparison to other cognitive disorders. Research studies included in this review and meta-analysis focused on analyzing differences between BD and MCI, or BD and dementia, on objective cognitive assessments to evaluate cognitive performance between the samples. Our original research, presented in Chapter 3, in contrast, focused on investigating differences in subjective cognitive complaints between individuals recently diagnosed with BD and Major Depressive Disorder (MDD), also taking into consideration the current mood stability of the participants (euthymic or in acute mood episode). The main finding from this thesis is that cognitive impairment is a serious outcome of BD that is on par with other cognitive disorders and evident even in the beginning and during euthymic stages of the disorder. Thorough implications of these findings are discussed in the remainder of this chapter.

Clinical Implications of Cognitive Deficits in BD vs MCI/Dementia

The systematic review and meta-analysis presented in Chapter 2 consisted of a total of 4 original studies, 2 of which compared BD and MCI, and 2 compared BD and dementia. The two comparisons provided clearer insight regarding which cognitive domains are affected in similar fashion to other known cognitive disorders.

The two studies comparing BD and MCI (Osher et al., 2011; Silva et al., 2009) had each assessed multiple cognitive areas, of which 3 cognitive domains were of interest in both studies: motor initiative, delayed memory recall, and visuoconstructional abilities. Our first meta-analysis on assessments across both studies found that motor initiative is significantly more impaired in BD in comparison to MCI (see Chapter 2, Figure 2A). The findings from our meta-analysis are consistent with previous research suggesting the presence of psychomotor difficulties in BD showing slower reaction times in affected individuals compared to HCs (Morsel et al., 2015; Burdick et al., 2009). However, studies included in our meta-analysis were comparing BD to another disorder where psychomotor impairments may be expected, yet still found significantly greater motor deficits in BD relative to MCI. Intriguingly, psychomotor dysfunctionality was evident in euthymic BD in both studies described in Chapter 2 (Osher et al., 2011; Silva et al., 2009), suggesting it may be a reliable clinical indicator of cognitive impairment as a result of BD. The persistence of psychomotor deficits across different stages of BD could imply serious functional complications developing with the progression of the disorder, which should be clinically addressed as early as possible.

From the further comparisons between BD and MCI, our meta-analyses did not find any significant differences in delayed memory recall between the two clinical populations (see Chapter 2, Figure 2B). Delayed memory recall difficulties are common in people with MCI, and appropriate diagnostic tests have been identified to correctly assess memory deficits in MCI (Kazui et al., 2005). Memory impairments have also been well-established in BD in comparison to HCs (Bearden et al., 2006), but findings from the meta-analysis presented in this thesis suggest these impairments may be on the same level as those seen in MCI. In addition, similar level of impairment between the two groups was seen in visuoconstructional abilities, once again indicating similarities in the magnitudes of impairment in the same cognitive areas between the disorders (see Chapter 2, Figure 2C). These findings could also be meaningful in further improving our understanding of cognitive impairments seen in BD, providing an estimate of the expected range of deficits in memory and visuospatial capabilities. The comparisons between BD and MCI give us a sense of how cognitive deficits found in euthymic BDs rank relative to those in adults with MCI, with a special focus on commonly affected cognitive areas between the disorders. Understanding the similarities in impairments between BD and MCI is important, as both disorders carry an increased risk for developing dementia in the later stages of the disorders (Diniz et al., 2017; Forrester et al., 2016), and early interventions are recommended.

Intriguingly, findings from the comparison between BD and dementia indicated different results, where one study (Vivjerberg et al. 2017) found greater deficits in BD, and the second study found greater cognitive deficits in dementia (Aprahamian et al., 2014). However, it is highly important to note the differences in samples between the studies; Vivjerberg et al.

[2017] compared individuals with BD in a current mood episode and patients with Alzheimer's disease (AD), while Aprahamian et al., [2014] compared euthymic BDs and patients with behavioral variant frontotemporal dementia (bvFTD). The contrast in cognitive abilities and functionality during euthymia and acute mood episodes in BD has been established in previous literature, where individuals in a mood episode display greater dysfunctionality than euthymic BDs (Brady Jr et al., 2017; da Silva et al., 2015). Furthermore, the two different types of dementia included in our meta-analyses (bvFTD and AD) also contain distinguishing features in brain connectivity, and consequently differentiate in functionality across various cognitive domains (Hafkemeijer et al., 2015; Lima-Silva et al., 2013). Due to the differences across subjects with BD and subjects with dementia, we did not perform a meta-analysis comparing these groups, and further investigations with appropriate categorization of subjects would be very useful for understanding the similarities in cognitive deficits between BD and different types of dementia.

Clinical Implications of Subjective Complaints in BD vs MDD

Our original work presented in Chapter 3 focused on detecting differences between patients recently diagnosed with BD and patients with MDD on subjective cognitive complaints as evaluated with the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA). We categorized patients based on their diagnosis, as well as their current mood for more analogous comparisons of their subjective complaints during that period. Analyses from our study demonstrated higher COBRA scores in euthymic BD relative to euthymic MDD, suggesting a greater presence of self-perceived cognitive difficulties in euthymic patients recently diagnosed

with BD in contrast to euthymic MDDs (see Chapter 3, Figure 1). Considering the many similarities between the mood disorders, it is intriguing to notice a difference in the subjective experiences of patients with BD and MDD during remission, which is contrary to findings from previous studies with the same aim as our study (Svendsen et al., 2012; Miskowiak et al., 2012). More specifically, the differences between the 2 groups were found among the euthymic patients, which could be indicative of serious aftereffects of mood episodes in BD relative to MDD. While cognitive and mental instability is evident during the course of a mood episode (Martínez-Arán et al., 2004), signs of subjective cognitive difficulties during euthymia may imply long-lasting effects of the mood episodes, usually resulting in worse clinical outcomes of the disorder (Sparding et al., 2015; Baune & Malhi, 2015).

Adding to the significance of the difference found between euthymic patients is the narrow inclusion criteria constricted to *recently diagnosed* patients with BD (within the last 3 years), enabling us to evaluate the presence of subjective complaints early after a diagnosis of BD. The greater manifestation of difficulties as reported by euthymic BDs in comparison to euthymic MDDs suggests that even in the beginning of the illness, patients with BD experience cognitive symptoms that affect their overall functioning. Individuals with good cognitive insight of their impairments are able to help in predicting the clinical outcomes of their disorder, perhaps due to their beliefs in the extent to which they are affected by the mood episodes (Martínez-Arán et al., 2005). Early detection of these difficulties and beliefs is important, as it can be clinically addressed earlier in the course of the disorder, and potentially prevent the development of worse clinical consequences with the progression of BD.

Furthermore, another part of the aim of the study presented in Chapter 3 was the detection of subjective complaints using the COBRA, an assessment specifically designed for identifying cognitive difficulties found in BD (Rosa et al., 2013). The COBRA is a fairly new cognitive assessment relative to many others, but it has recently been recognized as the best and recommended tool for assessing subjective cognition by the International Society of Bipolar Disorder (ISBD) cognitive task force (Miskowiak et al., 2018). This is a huge recognition, considering the number of clinicians worldwide that follow and respect the recommended guidelines by the ISBD. However, to our knowledge, this was the first original study assessing subjective cognitive differences between recently diagnosed BD and MDD through the use of the COBRA. Previous studies relied on the use of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), which is a shorter questionnaire put together using the most common self-perceived cognitive impairments across many psychiatric disorders (Fava et al., 2009). Due to the explicit relationship between BD and the COBRA, results from the study presented in Chapter 3 could be of greater significance for future clinical approaches to subjective cognitive complaints in BD.

Importance of Early Interventions on Cognition in BD

The studies presented in Chapter 2 and 3 of this thesis together highlight the importance of early detection and addressing of cognitive dysfunctionality in BD. Findings from the systematic review and meta-analyses (Chapter 2) point to the notion of increased similarities in cognitive deficits between BD and cognitive disorders in the later stages of BD. In

addition, analyses from the original work evaluating subjective complaints (Chapter 3) indicate the presence of self-perceived cognitive deficits shortly after the onset of BD, suggesting negative cognitive effects even at the beginning of the disorder. Findings from both studies signify the importance of evaluating cognitive functionality in the early phases of BD. Early examination of the cognitive abilities in BD would allow for more time and effort in preventing the possible outcomes with the progression of the disorder. Even within the first years following a diagnosis of BD, cognitive instability is evidently a crucial factor for the overall quality of life in affected individuals, leading to psychosocial and functional deficits in the beginning of the illness (Mackala et al., 2014). The risk of developing detrimental cognitive deficits in BD, as seen in dementia, increases through the aggregating effects of each additional mood episode (Diniz et al., 2017; Forlenza & Aprahamian, 2013). Neglecting the cognitive concerns (objective and subjective) in the early stages of BD could cause further complications in the later stages of BD. Hence, early cognitive evaluations and cognitive treatment strategies, such as family intervention, Cognitive Behavioral Therapy (CBT), and psychoeducation (Vieta et al., 2013), are crucial in preserving the cognitive well-being of patients with BD and preventing distressing clinical outcomes of the illness. Moreover, findings from recent trials suggest that Cognitive Remediation therapy (CRT) is another feasible treatment option for individuals with BD, which may enhance their cognitive abilities and overall functioning (Strawbridge et al., 2019). A combinative strategy consisting of the above-mentioned therapies in the early stages of BD may help in preserving the cognitive functionality of the individuals.

Strengths, Limitations and Future Directions

Two separate studies with distinct aims were presented in the current thesis. The systematic review and meta-analyses presented in Chapter 2 is the first study comparing cognition in BD relative to MCI and dementia, providing important insight of the similarity in affected cognitive areas, and the severity of impairment in BD. In addition, the studies included in this review and meta-analysis were regarded to be of high-quality, as assessed with the Newcastle-Ottawa Quality Assessment Scale (NOQAS). However, a main limitation of the study, which should be addressed in future work, was the combined grouping of BD patients in different mood states (euthymia and acute mood episode) and of different types of dementia (bvFTD and AD), for observing cognitive differences between BD and dementia. The review and meta-analyses also included a small number of studies (4), which may exaggerate the findings from these meta-analyses.

The original study presented in Chapter 3, to our knowledge, is also the first study comparing subjective cognitive complaints in patients recently diagnosed BD with patients with MDD. Another important strength of this study is the use of the COBRA, which is recognized as the most effective assessment tool for subjective complaints by the ISBD cognitive task force. The main limitation of this study, however, was the disproportional and limited sample size of patients with BD. Future studies evaluating subjective cognition in BD should increase the sample size, and consider a greater amount of variables that could play a role in the differences found in our study.

Conclusion

The main objective of the thesis was to compare the subjective and objective cognitive deficits in BD to those of other disorders with similar cognitive impairments. Findings from the systematic review and meta-analyses presented in Chapter 2 suggest that several cognitive areas in BD manifest the same severity (delayed memory and visuoconstructional abilities), or even greater (motor initiative), than seen across the same cognitive areas in people with MCI. In addition, findings from the comparison between BD and dementia were contradictory, depending on the mood state in BD and type of dementia. Finally, findings from the original study presented in Chapter 3 demonstrate a difference in subjective complaints between BD and MDD, where euthymic patients recently diagnosed with BD reported greater scores on the COBRA than euthymic MDDs. The higher presence of subjective complaints found in the early phases of BD in comparison to MDD is indicative of the severe difficulties experienced by individuals with BD, even in the beginning of the illness. These findings together highlight the importance of early detection and intervention addressing cognitive deficits in BD, with the aim of preventing further degradation in cognitive functionality throughout the course of the disorder.

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