Hidden beneath the surface of bipolar disorder: cognitive processes underlying movement

Onderliggend aan het klinisch beeld van de bipolaire stoornis: cognitieve processen betrokken in beweging

Thesis submitted for the degree of doctor in Medical Sciences at the University of Antwerp to be defended by

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Chapter 1

General introduction and outline

Bipolar disorder

Bipolar disorder (BD), previously referred to as manic-depressive illness, is amongst the most severe psychiatric disorders. It is typically characterized by cyclic episodes of mania and depression (or an episode with mixed features) which are separated by periods of clinical remission, or euthymia. The estimated prevalence of BD is approximately 1.5% to 3% of the general population (Murray and Lopez 1996; Merikangas et al., 2007; ten Have et al., 2002). Importantly, individuals with BD often have very poor psychosocial and occupational functioning (Fagiolini et al.,2013) with remarkable unemployment rates averaged at 55% in patients with BD, despite over 13 years of education (Altshuler et al., 2007; Dickerson et al., 2004) and severe impairments in home functioning and problematic relationships (Godard et al, 2011).

Bipolar Disorder type I or BD-I is the most severe form of the disorder. According to the Diagnostic and Statistical Manual of Mental disorders (DSM-5; APA 2013) only one acutely manic or mixed features episode is sufficient to diagnose BD I (although patients commonly also present with episodes of major depression). BD type II or BD-II is less severe than BD I and requires that patients experience at least one episode of hypomania and one episode of major depression (APA 2013). Out of patients with BD-I, 14-53% have rapid cycling, a clinically specific course of the illness defined as more than four mood episodes during a year (Tondo and Baldessarini 1998).

The specific criteria according to the DSM 5 for a manic episode are that patients have abnormally elevated or irritable mood and a required change in activity or energy that persists for at least one week (DSM 5; APA 2013). In addition, three or more of the following criteria apply; inflated self esteem and feeling of grandiosity, decreased need for sleep whereby they feel rested after only a few hours of sleep, psychomotor agitation, more talkative or pressured speech, racing thoughts, highly distracted, increased motivation, impulsivity and pleasure-seeking behavior. Hypomania is less severe than mania and does not cause a marked impairment in

social or occupational functioning and only needs to be present for 4 days. The specific criteria for a major depressive episode are that patients firstly have a depressed mood or loss of interest or pleasure (anhedonia) that persists for 2 weeks. In addition, five or more of the following symptoms must be present for 2 weeks: weight loss or weight gain or change in appetite, trouble sleeping or excessive amounts of sleep, fatigue, loss of energy, impaired self-esteem, less generative thoughts, inattentive, constricted behavior, slowed movements or psychomotor agitation and recurrent thoughts of death. The criteria require that the symptoms present in BD are not due to any other underlying issue such as substance abuse or a medical condition such as hyperthyroidism.

In other words, in addition to affected mood during acute episodes of BD, physical biorhythms and thought patterns are disrupted. Extreme episodes of mania or depression can lead to psychotic symptoms (Keck et al., 2003) and BD often includes additional co-morbidities such as anxiety disorders and substance abuse (Goodwin and Jamison 1990). Decline in cognitive capacity is additionally a major symptom of BD, with substantial effects on quality of life and overall functioning of the patient (Martinez-Aran et al., 2004).

Cognition in bipolar disorder

Historically, Kraepelin (in 1896) distinguished BD from schizophrenia on the basis that schizophrenia is chronic in nature (with cognitive deficits acknowledged as a core feature of the disorder) while BD is episodic with cognitive and symptom-free functioning between episodes. This view that patients with BD had full recovery between episodes persisted for many decades. However, there is abundant evidence since the late 1990s that the course of BD is also chronic in nature (Goodwin and Jamison 2007) and often presents with numerous mood episodes and residual mood and cognitive symptoms persisting in between mood episodes (Judd et al., 2005) indicating that the recovery in BD is not complete. In fact, it has been demonstrated

that although more than 97% of individuals with BD receiving treatment achieve clinical remission (no longer meeting DSM criteria for mania or depression) within 2 years, only 37% of patients have full functional and occupational recovery (Tohen et al., 2000).

In recent years, there has been a substantial increase in studies investigating cognitive dysfunction in BD while they are euthymic. Studying individuals in a euthymic state allows the identification of state-independent abnormalities that may be more related to the pathophysiology of the disorder. While mood stability is generally the goal in treatment of BD, additional research and knowledge relating to cognitive dysfunction in the absence of mood episodes may further our understanding of the pathophysiology of the disorder which may have important implications for treatment development.

Although cognitive impairments in BD have been previously regarded as limited to the affective episodes, it is now widely recognized that deficits persist in euthymia and these include psychomotor slowing, difficulties in executive functioning, declarative memory, visual memory and attention (Bora et al., 2010; Lopes et al., 2012; Bora et al., 2009; Bearden et al., 2001; Robinson et al., 2006). These impairments limit individuals with BD in their abilities to plan activities, set goals, monitor their behavior and cope with life stress (Martinez-Aran et al., 2004) and have been shown to additionally contribute to functional and occupational disability of the patients (Wingo et al., 2009). In addition, these deficits become more severe as the illness progresses (Robinson and Ferrier 2006), thus in addition to mood episodes, cognitive disturbances clearly play an essential role in the clinical identity of the disorder.

Psychomotor functioning

Deficits in psychomotor functioning are classic features of BD (Cornell et al., 1984; Sobin and Sackeim 1997; Buyukdura et al., 2011), and as mentioned, are

possible criteria for the diagnosis of mania and depression (DSM-5). Some individuals with BD experience psychomotor agitation. This manifests itself clinically as a state of restless behavior, where there is a need to move purposelessly. For example, individuals may pace up and down or show fidgety behavior (Parker et al., 1993). Other individuals with BD experience psychomotor slowing which is an observed slowing of both motor and mental functions, such as reduced speed, slowed speech or delayed motor initiation (Parker et al., 1993). In addition to psychomotor agitation and slowing, the psychomotor construct is broad and reflects diverse signs and symptoms. These disturbances include catatonia, neurological soft signs (NSS) and drug-induced extrapyramidal symptoms (EPS). Catatonia is a psychomotor syndrome that includes abnormal motor behavior and abnormalities in volition and affect. It is characterized by immobility whereby individuals may hold rigid poses (stupor), be unable to speak (mutism) or may have repetitive movements or phrases. Catatonia may also manifest itself in an excited variation whereby individuals perform abnormal non-goal oriented hyperactive movements (see Taylor and Fink 2003). Catatonia can be present in any acute phase of the illness (Tandon et al., 2013) and is recognized as a feature of BD in DSM-5 with a specifier 'with catatonic features'. NSS refer to subtle impairments in sensory integration, motor coordination and the sequencing of complex motor acts and cannot be precisely localized in the brain (Buchanan and Heinrichs, 1989; Griffiths et al., 1998). The presence of NSS are commonly reported in BD (Nasrallah et al., 1983; Gureje, 1988; Dimitri- Valente et al., 2012) and has been demonstrated in euthymia as well (Goswami et al., 2006; Sharma et al., 2016). Patients with BD are also highly vulnerable to have antipsychotic-induced movement disorders (EPS) (Gao et al., 2008), which can include symptoms such as tremor, tardive dyskinesia (jerky movements), parkinsonism (such as rigidity), and dystonia (continuous spasms and muscle contractions).

As psychomotor disturbances encompass such a broad range of symptoms, based on previous research (Morrens et al., 2014), the term 'psychomotor functioning' will be used in this thesis to describe the contribution of all cognitive and

motor processes involved in movements. An activity is qualified as psychomotor when its performance can be measured by the speed and accuracy of the motor output. Although some motor skills are very basic and may be executed unconsciously, merely requiring the activation of motor units and the contraction of muscles, the majority of motor skills involve a broad range of cognitive processes that contribute to motor activity. In support of this, Willingham et al. (1998) and later Ridderinkhof et al (2004) describe a theory of motor skill learning that includes numerous neuro-cognitive processes involved in regulation of behavior during task performance, ranging from early planning stages, initiation and execution of movements as well as cognitive control. Each of the different components can be affected independently of one another (Morrens et al., 2006). In other words, psychomotor functioning involves elements in movement production (Rizzolatti and Luppino 2001) and perceptual processes and cognitive control of action (Buch et al. 2010; Duque et al. 2013; Kennerley et al. 2004; Ridderinkhof et al. 2004; Rushworth et al. 2004; Rushworth et al. 2005).

In this light, many of the cognitive impairments which have been proposed in euthymic BD may be directly related to the sub-processes involved in motor functioning. Specifically, in addition to impairments that are clinically manifested as psychomotor slowing, such as disturbances in planning and slowed execution of movements, executive control is essential for optimal outcome.

Inhibition is an important aspect of executive control that can be defined as the ability to suppress responses when they are inappropriate in a given context (Logan and Cowan, 1984) and is a critical element in task performance. The inability to inhibit responses relates to impulsive behavior, a clinically observable phenomenon in BD (Christodoulou et al., 2006). Extreme manifestations of impulsivity (for example excessive drug abuse and even suicide attempts) impair everyday functioning and represent important targets for treatment interventions (Evenden, 1999; Moeller et al., 2001).

Another important aspect of executive functioning necessary for optimal performance is performance monitoring, also referred to as action or conflict monitoring. It involves continuous monitoring of behavior and making subsequent behavioral changes when adjustments are required. Successful performance monitoring has important implications for daily life functioning (Ullsperger et al., 2006); individuals may experience problems in flexibly adjusting their behavior, which is essential for goal-directed behavior, and in turn these problems may interfere with treatment compliance.

Although there is evidence of psychomotor dysfunction persisting in euthymia (Arts et al., 2008; Bora et al., 2009), the term psychomotor slowing is most often confused and used interchangeably with reduced processing speed. Studies that have investigated psychomotor slowing in BD have used simple measures relating to motor speed or measures relating to a reduction of information processing speed as opposed to the broader term of psychomotor slowing used in this thesis which encompasses the slowing of all cognitive and motor sub-processes involved in movement. In addition, inhibition and performance monitoring clearly have important implications in BD; however whether or not BD patients in a euthymic state have difficulties in these areas remains unclear. The focus of this research is to further knowledge in the gaps of cognitive symptoms relating to psychomotor functioning in euthymic BD. Specifically, psychomotor slowing (reflected in the planning and execution time of a movement), inhibition of unwanted behavioral output, error detection and monitoring behavior will be investigated.

Assessment methodology

As mentioned, studies that have investigated psychomotor slowing in bipolar disorder have used measures relating to information processing speed or motor speed. Our research group has developed a technique that allows different

components relating to psychomotor functioning to be objectively measured (Hulstijn et al., 2002). The technique involves drawing lines and figures which are presented on a computer screen as quickly and as accurately as possible on a piece of paper placed on a digitized writing tablet. An electronic digitizer and specially designed electronic pen allow the measurements of initiation time, stimulus re-inspection time and duration of movement time, allowing a distinction between cognitive and motor components during a task. Using these behavioral measures will allow further understanding of the nature of proposed psychomotor slowing in BD.

In addition to behavioral measures, on a neurophysiological level, event-related potentials (ERPs), derived from the electroencephalogram (EEG) during performance of a task, represent activity occurring during distinct cognitive stages. This methodology has the advantage of high temporal resolution (in milliseconds), allowing different electrophysiological components to be observed, each representing distinct cognitive sub-processes occurring during a task (Nunez 1981). With the help of ERPs, understanding the neural underpinnings relating to the processes of inhibition and performance monitoring during a task can help further our knowledge relating to these proposed deficits in BD.

Inhibitory control can be investigated using a task such as the Go/NoGo task. This computerized task consists of visual presentation of frequent stimuli, which require a motor response (Go), interspersed with infrequent stimuli, which require the inhibition of the prepotent response (NoGo). At an early stage of the inhibition process, around 200 msec following the presentation of a NoGo stimulus, an enhanced negative peak appears in the ERP. This is known as the NoGo N2 and has been proposed to reflect the detection of conflict between an internal representation of a Go and a NoGo response (Nieuwenhuis et al., 2003; Donkers and van Boxtel 2004). Using source localization, the NoGo N2 has been shown to be generated in the anterior cingulate cortex (ACC) and the inferior frontal cortex (IFC) (Lavric et al., 2004; Pliszka et al., 2000; Bokura et al., 2001). At a later stage of the inhibition process, an enhanced positive peak is elicited in the ERP around 300-500

msec following the NoGo stimulus. This later component is referred to as the NoGo P3 and believed to be related to the actual inhibition of the motor system (Kok et al., 2004). The NoGo P3, which is measured from the frontocentral scalp, has been shown to be generated in the orbito-frontal cortex (Bokura et al., 2001) (which differs from the central-parietal scalp location during a Go trial). These two distinct components of the ERP have been consistently linked to response inhibition. Unfortunately, literature on cortical activations relating to inhibition in BD is sparse and inconclusive, thus using the ERP methodology to investigate inhibition can lead to greater understanding of the sub-processes of inhibition.

Error detection is a crucial process of performance monitoring ensuring that more cognitive control is used in the future to improve performance (Carter et al., 1998). A replicable effect is that following an error, individuals respond slower on the subsequent trial (Rabbit 1966), referred to as post-error slowing. The Eriksen Flankers task (Eriksen and Eriksen 1974) is often used to investigate performance monitoring. It is a choice reaction time task whereby it is necessary to respond quickly and many errors are often made. When an error is made, a sharp negative peak appears in the ERP around 50 to 100 msec following the error, known as the error related negativity (ERN) or the error negativity (Ne) (Gehring et al., 1993; Falkenstein et al., 1990). Using source localization and fMRI (Dehaene et al., 1994; Van Veen and Carter 2002; Ullsperger and Von Cramon, 2006) it has been shown that the ERN is generated in the anterior cingulate cortex (ACC). In other words, on a neurophysiological level the ERN reflects an early stage of performance monitoring and ACC activations in the brain during the production of errors. Although a lot of attention has been given to the underlying neural underpinnings relating to performance monitoring in other major psychiatric disorders, there is little information regarding performance monitoring using ERN in BD.

Outline of the thesis

The main aim of the thesis is to develop greater understanding of cognitive deficits which have been proposed to be present in the euthymic stage of BD as they may be related to the pathophysiology of the disorder and may be important treatment targets. Specifically, different aspects of psychomotor functioning in BD are investigated. This includes an investigation of impairments that are clinically manifested as psychomotor slowing (reflected as disturbances in planning and execution of a task), as well as an investigation of two cognitive control processes that are necessary for successful movement, inhibition of unwanted behavioral output and performance monitoring.

Chapter 2 of the thesis begins investigating psychomotor functioning in BD using behavioral measures. This chapter presents a study that compares a group of individuals with BD in a euthymic state with matched healthy controls. Drawing tasks with varying levels of difficulty were performed using a digitized writing tablet. This behavioral method has not previously been used in BD and allows difficulties in cognitive and motor component of a movement to be distinguished from one another in order to further understand the nature of psychomotor slowing present in BD. Previous studies have demonstrated a slowing of both motor and cognitive components in MDD (Van Hoof et al., 1998) and in individuals with schizophrenia who were hospitalized (Van Hoof et al., 1998; Jogems-Kosterman et al., 2001). Interestingly, a different pattern of cognitive slowing without motor slowing was demonstrated in stabilized schizophrenia (Jogems-Kosterman 2004; Morrens et al., 2006). The hypothesis of the study is that patients with BD in a euthymic state will have cognitive slowing but motor slowing will be intact, similar to previous findings in stabilized schizophrenia.

Chapters 3-5 of the thesis delve into electrophysiological evidence of aberrant event related potentials in BD and their functional significance. As an introductory chapter in understanding the usage of electrophysiological measures to

further understand neurobiological correlates underlying abnormal behavior, **Chapter 3** presents a systematic literature review of the available ERP data in euthymic BD. The review focuses on the functional significance of abnormal ERP activity present in BD and examines clinical and medication influences on the ERP.

Chapter 4 provides an investigation of two ERP components reflecting sub-processes of inhibition, the NoGo N2 and NoGo P3, using a simple task, as this has not yet been investigated in BD. Patients with BD in a euthymic state and a group of matched healthy controls performed a Go/NoGo task and the ERPs reflecting inhibitory control were compared. Although behavioral abnormalities in inhibitory control have been demonstrated in BD (Torralva et al., 2011; Frangou et al., 2005), studies that employed easier tasks (with less cognitive demands) did not observe abnormal inhibitory control in euthymic BD (Ibanez et al., 2012; Townsend et al., 2012). The hypothesis of the study is that patients with BD in euthymia will have normal performance on a simple inhibition task. Regardless of behavioral performance, cortical abnormalities have been consistently observed in BD (Hajek et al., 2013). Therefore, this study also hypothesizes that differential neural activations relating to inhibitory processes will be observed in BD compared with controls.

Chapter 5 is the first study to date to investigate performance monitoring as reflected in the ERN in BD. A group of euthymic BD patients and matched healthy controls performed a flankers task. ERPs reflecting performance monitoring were compared. Reduced ERN amplitudes have been demonstrated in individuals with schizophrenia (Bates et al., 2002; Houthoofd et al., 2013). Given clinical and cognitive similarities between BD and schizophrenia, the hypothesis is that individuals with BD in a euthymic state will have reduced ERN amplitudes, implying difficulties in error detection and monitoring of ongoing actions.

Chapter 6 provides an updated comprehensive review and evaluation of the available evidence-based trials of pharmacotherapy for the treatment of BD I**.** The purpose of this review in the thesis is to highlight that current treatment strategies are targeted towards rapidly treating acute manic or depressive episodes and

stabilizing mood and not on cognitive abnormalities. Stabilization includes preventing relapse of a mood episode or reducing the frequency of episodes or the severity of symptoms (and sub threshold symptoms) in order to enhance social and occupational functioning. However, treatment remains a challenge due to the complexities of BD. A large range of factors need to be considered when choosing between treatment options such as the phase of the illness (acute episode or maintenance), symptoms (mania or depression), rapid cycling, polarity, psychiatric and somatic co-morbidities and psychotic and cognitive symptoms. In addition, (long term) efficacy and side effects of medications need to be taken into account, as drug tolerance which typically is a challenge with mood stabilizing drugs, has a large impact on treatment adherence (Bates et al., 2010).

The final chapter (**Chapter 7),** a general discussion, will provide a summary of the findings reported in each chapter and discuss these findings in light of previous research and further elaborate on the findings. Limitations and implications for future research are discussed.

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Chapter 2

Unraveling psychomotor slowing in bipolar disorder

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Abstract

Background/Aims

In addition to affective and cognitive symptomatology, psychomotor deficits are known to be present in bipolar disorder (BD). Psychomotor functioning includes all of the processes necessary for completing a movement, from planning to initiation and execution. While these psychomotor symptoms have been studied extensively in schizophrenia and major depressive disorder, only simple measures have been conducted in BD. The present study examines psychomotor functioning in bipolar disorder.

Methods

22 euthymic bipolar disorder patients and 21 healthy controls performed three computerized copying tasks varying in cognitive load. Movement times (MT), reflecting fine motor processing and initiation times (IT), reflecting cognitive processing of visual-spatial information were separately measured in each group.

Results

The BD patients had longer ITs but not MTs in the most simple task and the opposite pattern of longer MTs but not ITs in the complex task. However, when controlling for residual mood symptoms, the MTs were no longer significantly slower in the BD group.

Conclusions

The longer MTs and ITs in BD reflect overall psychomotor slowing. Specifically, the results provide evidence for cognitive slowing in BD. In addition, the longer MTs in the complex task reflect a slowed motor component of movement when the cognitive load is high and when depressive symptoms are present. These findings extend the current knowledge of the nature of psychomotor slowing in BD and may have important prognostic implications for the patients.

Introduction

Apart from mood episodes, patients with bipolar disorder (BD) experience a wide range of cognitive disturbances both in the acute stages of the illness and in remission (Bearden et al., 2001). Psychomotor functioning has repeatedly been proposed to be impaired in bipolar disorder, both in symptomatic states of the disorder (manic and depressed) (Burdick et al., 2009; Malhi et al., 2007) and in euthymia (Arts et al., 2008; Bora et al., 2009).

Psychomotor slowing (PS) is often confused with reduced processing speed. Although these two processes overlap, speed of psychomotor functioning should be clearly delineated from processing speed (Morrens et al., 2008a; Morrens et al., 2006). Processing speed refers to the rate in which cognitive processes are executed (Lezak 1993). In contrast, psychomotor functioning can be defined as all of the processes necessary to complete an action, from planning to initiation and execution of an action. Importantly, studies have demonstrated that different components involved in psychomotor functioning can be affected independently, including the planning and initiation processes involved in movements (cognitive components) as well as their execution (motor component) (Morrens et al., 2006).

As a result of this confusion, PS in BD has typically been evaluated using tasks that measure processing speed (see Bora et al., 2009 for a review). Specifically, studies have used the Trail Making Test (TMT-A; Reiten 1958) and the Symbol-Digit-Substitution Test (SDST). While both of these tasks have been labeled as evaluating PS (Kalra et al., 1993), these tasks are in fact more sensitive to processing speed and are not ideal tasks for the assessment of PS. In addition these tasks also gauge different higher order cognitive processes such as working memory and attention.

PS in BD has also been evaluated by the use of simple motor tasks (i.e., finger tapper or grooved pegboard) with some (Malhi et al., 2007; Zubieta et al., 2001; Varga et al., 2006) studies demonstrating slowed motor functioning in euthymia. Importantly, these simple measures used to investigate psychomotor functions in BD do not allow a

separation of the different components involved in PS. In other words, studies investigating speed of psychomotor functioning apart from traditionally measured cognitive deficits in BD have been limited by the use of simple and inadequate measures.

Sophisticated experimental methods have been developed using computerized copying tasks in order to differentiate between sensorimotor and cognitive components involved in the generation of speeded movements. These methods have been found to be objective and reliable in the investigation of psychomotor activity and have been used in other major psychiatric disorders including MDD (Pier et al., 2004a; Sabbe et al., 1996; Sabbe et al., 1999; Schrijvers et al., 2008a), anorexia nervosa (Pieters et al., 2003; Pieters et al., 2006), alcohol dependence (De Wilde et al., 2008) and schizophrenia (Morrens et al., 2006; Jogems-Kosterman et al., 2001; Jogems-Kosterman et al., 2006).

While only simple measures of psychomotor symptoms have been conducted in BD, psychomotor functioning has been studied extensively in schizophrenia and major depressive disorder, two disorders that share a very similar clinical and cognitive profile with BD. Studies have demonstrated PS to be an intrinsic part of both MDD and schizophrenia (Schrijvers et al., 2008b; Morrens et al., 2007; Morrens et al., 2008b), but demonstrated a different PS structure between these illnesses. Using the computerized writing tasks, Van Hoof et al (1998) demonstrated that patients with MDD presented with both motor and cognitive slowing, while stable patients with schizophrenia were only slow in the cognitive components. Similarly, Jogems-Kosterman et al (2001) found cognitive slowing in schizophrenia and not motor slowing in stabilized schizophrenia patients. However, later studies found both motor and cognitive slowing in inpatients in a more acute stage (Morrens et al., 2006; Jogmes-Kosterman et al., 2004). These dissociable abnormalities of the different psychomotor components further suggest that the subprocesses are distinct and may be dissimilar in different disorders, and may be state related. Thus, these studies highlight the importance of investigating the different subprocesses of psychomotor functioning. Given the reported importance of

disturbances in psychomotor functioning and the impact on functional outcome in depression and schizophrenia, it is essential to gain a better understanding of psychomotor activity in BD. In addition, using sophisticated measures in BD will enable an investigation into the nature of PS in BD.

The present study investigated psychomotor functioning by use of computerized fine motor performance analysis in patients with BD in a euthymic state compared with healthy controls. Subjects had to copy single lines, simple and complex figures. By using a digitized writing tablet, precise measurements of the different psychomotor processes involved in making a movement can be made, specifically the speed of initiation and execution of a movement. In addition, cognitive load was manipulated by increasing the complexity of each task. In this way, the interaction between cognitive and motor functioning in BD can be investigated. It was hypothesized that cognitive processes related to movements will be slowed in BD, just as in stabilized schizophrenia patients, and motor speed processes will be spared.

Method

Subjects

Twenty two inpatients and twenty one healthy controls were recruited for the study. All participants were between the ages of 18 and 65. Patients with a DSM-IV-TR diagnosis of BD, as assessed by a semi-structured interview were included. Clinical evaluation of the patient group was done by means of the Hamilton depression rating scale (HDRS; Hamilton 1960) and the Young Mania Rating Scale (YMRS; Young et al., 1978). A maximum score of 8 on the HDRS indicating the absence of depression and a maximum score of 6 on the YMRS indicating the absence of mania was necessary for inclusion in order to obtain a sample of euthymic BD patients. All participants were also assessed for residual depression symptoms using the Beck Depression Inventory (BDI-II; Beck et al., 1961). Patients with other

disorders that could be related to neuropsychological impairment (significant physical or neurological illness, a history of head injury, substance abuse or dependence in the last year, mental retardation) were excluded from the study.

The control group consisted of healthy volunteers who were matched to the patient group according to age, gender and education level. Control participants completed the same clinical rating scales as the patients.

All participants gave their written informed consent. The study was carried out in accordance of the latest version of the Helsinki Declaration and was approved by the medical ethics committee of the participating hospitals.

Apparatus and tasks

Digitizing tablet

The following writing tasks were administered by means of a Digitizer Graphics tablet (WACOM1218RE) and a special pressure-sensitive pen connected to a standard personal computer.

Writing tasks

For the following writing tasks, participants had to copy lines or figures presented on a computer screen as fast as possible on a sheet of paper placed on the writing tablet. See figure 1 for an illustration of the task stimuli.

Line copying task (LCT)

Participants were presented with straight horizontal, vertical or diagonal (2 orientations) lines. Each participant copied 24 lines. This comprised of four different lines each presented six times in a random order.

Simple figure copying task (FCT-S)

Participants were presented with a series of very simple figures (such as a circle or diamond). As in the LCT, there were 24 figures comprising of four simple figures each presented six times in a random order.

Complex figure copying task (FCT-C)

A series of 12 different complex figures were presented. These figures varied in complexity and were divided equally into 3 different levels of familiarity (letters, familiar figures and unfamiliar patterns) with 4 stimuli in each condition. In order to additionally manipulate the complexity of the figures, each stimulus type was further subdivided and presented with either 4 or 8 lines. As the figures in this task were difficult to remember, there was an option to re-inspect the figure if necessary.

Procedure

The procedure used to assess the writing tasks is described in full in Morrens and colleagues (2006). For further details of the LCT, FCT-S and FTC-C, see figure 1.

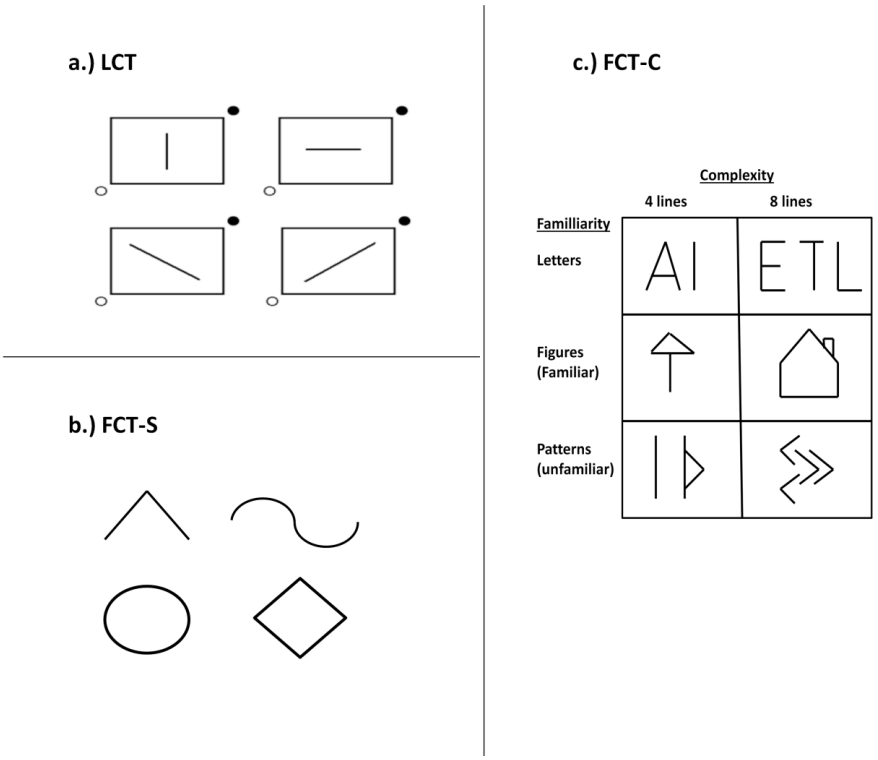

Figure 1: Stimuli presented in the line copying task (LCT), simple figure copying task (FCT-S) and complex figure copying task (FCT-C). Subjects were required to copy the lines or figure as quickly as possible. The complex figures varied in complexity and familiarity.

Statistical analysis

For each task, two measures were calculated. Firstly, the time between the presentation of the stimulus and the start of the first drawing (initiation time; IT), reflecting the cognitive processes involved such as the preparatory process, stimulus evaluation, response selection and organization. And secondly, the time between the start of the first movement and the completion of the last movement (movement time; MT), reflecting fine motor processes. The time taken to re-inspect the figure in the FCT-C was also measured (re-inspection time; RT). Mean ITs, MTs and RTs were calculated for each subject for all analyses.

Statistical analyses were performed using SPSS 20.0 A repeated-measures General Linear Model (GLM) was conducted with Group (BD patients and controls) as the between subjects factor and Complexity (LCT, FCT-S, FCT-C) as the within-subject factor. Separate analyses were conducted for IT and MT.

In addition, separate analyses were done on the FCT-C as cognitive load was most explicitly manipulated in this task. A repeated-measures GLM was carried out with Group (BD patients and controls) as the between subject factor and Familiarity (Letters-Patterns-Figures) and Number of Lines (4-8) as within subjects factors.

For the analysis of the clinical variables, ANOVA (in cases of continuous variables) or Chi-square tests were performed to compare frequencies. Medications were a possible confounding factor and this was examined in the patients group using Multivariate ANOVAs with each medication as a between subjects factor (Mood stabilizer, antidepressant, antipsychotic and benzodiazepine) and the three tasks as the Dependent variable. These analyses were done separately for ITs and MTs.

Results

Clinical variables

For an overview of the clinical variables, see Table 1. There were no statistically significant differences in the groups regarding age, education, gender or handedness. The YMRS, HDRS and BDI-II confirmed the euthymic status of all included patients, however, the scores of the euthymic patients did differ significantly from the healthy controls with higher scores on all three measures.

Table 1: Overview of demographic and clinical characteristics

	Bipolar disorder (n=22)	Control (n=21)	Test statistic	p-value
Gender	50% Male	38.1% Male	x^2=.617	0.43
Age, mean years (SD)	45 (13.98)	38 (15.76)	F=2.02	0.16
Education level (mean rank)	1.95	2.05	x^2=.206	0.90
Right handed	16 (73%)	19 (90%)	x^2=2.24	0.14
Clinical rating scale, mean (SD)				
YMRS	2.35 (2.06)	1.09 (1.81)	F=4.30	.045*
HDRS	3.25 (2.79)	0.62 (1.12)	F=16.02	.000*
BDI-II	10.75 (8.63)	3.76 (3.62)	F=11.65	.002*
Medication				
Mood stabilizer	18 (81.8%)			
Atypical antipsychotic	13 (59%)			
Antidepressant	7 (31.8%)			
Benzodiazepine	3 (13.6%)			

*p<.05, YMRS=Young Mania Rating Scale (Young et al, 1978), HDRS=Hamilton Depression Rating Scale (Hamilton, 1960), BDI-II= Beck Depression Inventory (Beck et al, 1996). Education level subdivided in a low (1), medium (2) and high (3) level in accordance with the Belgium education system.

Initiation time analysis

Table 2 depicts the ITs in each group for each task. Repeated measures IT analysis of all three tasks showed a significant main effect of Complexity *(*F[2,82]=121.474, *p*<.001), indicating that there was a difference in how long it took to initiate drawing, with the initiation times getting progressively longer as the task

got harder (LCT: *M*=.82 s, *SD*=.18; FCT-S: *M*=.84 s, *SD*=.19 and FCT-C: *M*=1.40 s, *SD*=.40). Within-subject pairwise comparisons showed that the difference in IT between the LCT and FCT-S was not significant *(t(*42)=-1.927, *p*=.061), but there was a significant IT difference between LCT and FCT-C *(t(*42)=-11.07, *p*<.001) and there was a significant difference between FCT-S and FCT-C *(t(*42)=-11.96, *p*<.001) .

There was no significant interaction between Complexity and Group *(F*<1), however there was a significant main effect of Group (*F*(1,41)=5.284, *p*=.027). BD patients had longer ITs indicating that they were slower to react from the time the stimulus was presented until the start of the movement *(M=* 1.09 s, *SD*=.30) than healthy controls *(M=*.95 s, *SD*=.18). Follow up analyses (Univariate ANOVA for each task individually) showed that significant Group IT differences were present for the LCT *(F[*1,41]=5.860, *p*=.020) and the FCT-S *(F[*1,41]=7.657, *p*=.008), but there were no significant IT differences between the groups during the FCT-C (*F*[1,41]=2.196, *p*=.146).

Movement time analysis

The movement times in each group are also depicted in Table 2. Movement time analyses of the three tasks showed that there was a significant main effect of Complexity (*F*[2,82]=357.706, *p*<.001). As the task became more difficult, subjects took more time to complete the task (LCT:.*M=*.37 s, *SD*=.14; FCT-S: *M=*.83 s, *SD*=.30; and FCT-C: *M*=2.81 s, *SD*=.87). Pairwise comparisons showed that there was a significant difference between LCT and FCT-S (*t*(42)=-11.40, *p*<.001), FCT-S and FCT-C *(t(*42)=-18.52, *p*<.001) and between LCT and FCT-C (*t*(42)=-17.86, *p*<.001).

There was a significant main effect of Group (*F*[1,41]= 8.86, *p*=.005). BD patients were overall slower than controls in their movement time (*M*=1.53 s, *SD*=.56 vs. *M*=1.14 s, *SD*=.32). In addition, there was a significant interaction between Complexity x Group (*F*[2,82]= 6.568, *p*=.002).Follow up analyses showed that there was a significant MT effect of Group for FCT-S (*t*(41)=3.11, *p*=.003) and FCT-C

(*t*(41)=.79, *p*=.008), but not in the LCT (*t*(41)=1.77, *p*=.085). In other words, when the task became more difficult, the MT of BD patients was much slower compared with controls.

Table 2: Initiation time (IT) and Movement time (MT) in seconds and the between subjects effects in all three tasks. Resinspection times (RT) are presented for the complex figure task.

	BD (n=22)	Control (n=21)	F(1,41)	p-value
LCT				
IT	.869 (.02)	.747 (.13)	5.86	.020*
MT	.404 (.16)	.327 (.13)	3.122	.085
FCT-S				
IT	.917 (.22)	.766 (.11)	7.657	.008*
MT	.981 (.41)	.672 (.20)	9.652	.003*
FCT-C				
IT	1.486 (.48)	1.308 (.29)	2.196	.146
MT	3.199 (1.10)	2.429 (.64)	7.763	.008*
RT	.194 (.23)	.144 (.20)	.215	.645

*p<.01, standard deviations are given in parentheses, LCT= line copying task, FCT-S= simple figure copying task, FCT-C= complex figure copying task

Manipulating cognitive load in the FCT-C

Explicit manipulation of cognitive load was done by increasing the Familiarity of the figures (letters-figures-patterns) and the Lines (4-8 strokes). See figure 2 for an illustration of the ITs in the FCT-C in all of the different conditions. Analysis of ITs showed that there was an overall main effect of Lines (*F*[2,82]=1.021, *p*<.001) and

Familiarity (F[2,82]=42.248, p<.001). There were significantly longer ITs when there were 8 lines compared with 4 lines and also longer ITs as the stimulus familiarity increased in complexity. In addition, there was a significant interaction between Lines and Familiarity (F[2,82]=17.131, p<.001). There was no significant main effect of Group (F[1,41]=2.196, p=.146) nor were there any significant interactions with Group (Lines x Group, Familiarity x Group or Lines x Familiarity x Group, all F<1). Although patients were consistently slower than healthy controls in every condition, the increase in IT did not differ significantly between the groups.

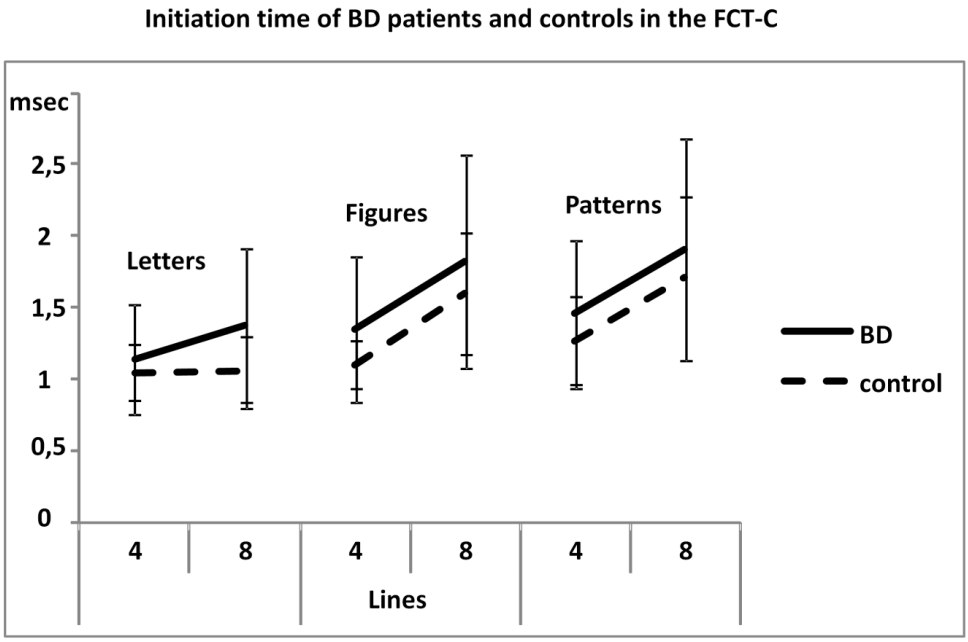

Figure 2: Initiation times of the Complex Figure Copying Task (FCT-C) of BD patients and healthy controls. Results for easy (letters), more difficult (familiar figures) and most difficult (unfamiliar patterns) stimuli are depicted.

Analysis of MT also showed significant main effects of Lines (F[1,41]=211.608, p<.001) and Familiarity (F[2,82]=87.089, p<.001). MT changed with Familiarity and ease of the drawing. In addition, there was a significant main effect of Group (F[1,41]= 7.932, p=.007). Patients were slower in their MTs than controls in this task. However, there were no significant interactions between Lines x Group (F[1,41]=3.878, p=.056), Familiarity x Group (F[2,82]=2.223, p=.115) or Lines x Familiarity x Group(F<1).

Reinspection of stimulus was also evaluated in the FCT-C and there was no significant main effect of Group (F<1), indicating that both groups needed to reinspect the stimuli the same amount of time (see Table 2).

Medication effects

MANOVAs were run in order to look for any effects of medication on the patients' performance. Between-subjects analyses revealed that mood stabilizers, antipsychotics or antidepressants did not have any significant impact on in the patients ITs and MTs in their task performance. Only 3 patients were taking benzodiazepines, but excluding the patients taking benzodiazepines did not influence any of the analyses.

Correlations with residual mood symptoms

Residual mood symptoms were found to be present in the BD patients, with significantly higher YMRS, HDRS and BDI-II scores. Correlation analyses between the clinical rating scales and the psychomotor variables were calculated in order to see which deficits may have been influenced by residual mood. The BDI-II scores were significantly associated with MT in the FCT-S (r=.44, p=.002) and in the FCT-C (r=.35, p=.013). However, there was no association between BDI-II scores and MT in the LCT (r=.20, p=.103). Additionally, there were no significant associations between BDI-II

scores and IT in any of the tasks (all r-values<.25, NS). The HDRS scores correlated significantly with the BDI-II scores (r=.68, p<.001) and therefore the same significant correlations between MTs in FCT-S and FCT-C, but not for the LCT were found. No statistically significant correlations were found between the YMRS and any of the psychomotor variables.

The presence of low level residual mood symptoms is common in euthymic BD (for example, Martinez-Aran et al., 2004) and has been found to impair cognition in affective disorders (Ferrier et al., 1999). Therefore, these group differences need to be ruled out. Statistically controlling for residual mood may cause the group differences to disappear. Covariate analyses were subsequently conducted on the MT of the FCT-S and FCT-C, as these correlated significantly with BDI-II and HDRS ratings. This was done in order to examine whether previously observed between-group differences on these factors remained when the effect of mood on performance was partialled out. When the effects of depressive mood on these variables were controlled for, the between-group effect disappeared (controlling for BDI-II scores; F[1,37]=1.606, p=.213], controlling for HDRS scores: F[1,37]=2.237, p=.143)(Method as in Thompson et al., 2005).

Discussion

This study examined speed of psychomotor functioning in BD. With the aid of a Digitizer Graphics tablet different sub-processes involved in generating speeded movements were measured. Specifically, cognitive and motor components of psychomotor functioning were distinguished.

As expected, patients with BD in a euthymic state showed more PS than healthy controls.

Using tasks that increased in cognitive load allowed insight into the nature of PS in BD. The MT of the simple lines is the best estimate of motor slowing as not much accuracy is required (the orientation of the line had to be correct but the

length did not matter) and the cognitive load of drawing one stroke is minimal. The MT in the LCT was not found to be slower in the BD patient group, indicating that pure motor (neuro-motor) processes are spared in euthymic BD (as in Malhi et al., 2007; Varga et al., 2006). In contrast, the longer ITs in the patients group during this task indicate slowed cognitive processes in BD.

Additional cognitive effort is required in the figure copying tasks. Interestingly, additional cognitive load led to longer MTs in the BD group as opposed to in the LCT. Although MTs mainly address motor activity, the MTs in the more complex tasks seem to grasp a certain load of cognitive processes as well. For example, there are some cognitive processes that occur during the execution of a movement, such as keeping the intended graphic output in working memory, retrieving and selecting the subsequent stroke and performance monitoring. While neuro-motor processes are spared, there is a slowed motor component of movement when the cognitive load is high.

The patients in this study were not clinically depressed, however they had low level residual depressive symptoms, reflected in higher BDI-II and HDRS scores in the patient group compared with the control group. While depressive symptoms may impair cognition (Ferrier et al., 1999), in addition, some studies have found specific associations between depression severity and PS in different major psychiatric disorders (Caligiuri and Ellwanger 2000; Iverson 2004) while others did not (Brebion et al., 1997; Lemke et al., 1997). The depressive symptoms in the present study correlated with MT in the figure copying tasks. In fact, the group MT difference disappeared when the depression scores were controlled. In other words, the slowed motor component of a movement which is present when the cognitive load is high is related to (subsyndromal) depressive symptoms in BD.

Results of this study are in line with previous findings in patients with schizophrenia and unipolar depression. The BD patients in this study had cognitive slowing unrelated to mood (as in schizophrenia) and additional slow MTs that were related to depression (as in MDD). As later studies found slowed MTs in acutely ill

schizophrenia patients (in addition to cognitive slowing) (Morrens et al., 2006; Jogems-Kosterman 2004) the additional slowed MTs might only be present in more severely affected patients and may be associated with their poor functioning.

It is possible that the motor slowing in the figure copying tasks may also be due to neurological soft signs that have been reported in BD (Goswami et al., 2006). Neurological soft signs are a group of neurological abnormalities that are non-localizable and include difficulties in motor coordination and complex motor sequencing (Heinrichs and Buchanan 1988). The added complexity of drawing a figure as opposed to a line may have tapped into these difficulties, especially motor sequencing difficulties, resulting in the slowed MTs in those tasks.

Cognitive deficits in bipolar disorder are known to be associated with significant psychosocial impairments (Zubieta et al., 2001; Martinez-Aran et al., 2004) and psychomotor slowing has been specifically found to be related to poor social, clinical and functional outcomes (in schizophrenia and depression) (Jogems-Kosterman et al., 2001; Green et al., 2004). Therefore, PS in BD is critically important as it may hinder daily life activities of the BD patient.

The findings of this study should be considered in light of the limitations of the study. First, all of the patients were taking medications and this may have influenced psychomotor functioning in BD. Analyses of our patient data however did not show any significant effects of medication on the motor or cognitive component, suggesting that they did not influence this data. In other words, it is unlikely that our results were confounded by medications. Second, the sample size used in this study is rather small to demonstrate significant group differences.

It is important to note that performance on the psychomotor tasks used in this study involves a large range of cognitive processes including attentional, perceptual and encoding processes, working memory, visuospatial processes and executive functioning (Jogems-Kosterman et al., 2001; Gazzaniga et al., 2014). Slowing can occur at any stage and unfortunately, it is not possible to distinguish between the contribution to slowing of these different cognitive processes.

Higher order cognitive functions have been shown to be linked to psychomotor functions. For example, performance monitoring has been linked to psychomotor functioning in depression (Schrijvers et al., 2008a); only patients with pronounced PS demonstrated impaired performance monitoring. Future studies should investigate the impact of psychomotor functions on executive impairments in BD. Brain imaging should also be conducted to investigate the areas of the brain affected by psychomotor deficits as this may add to the pathophysiology of the disorder.

Conclusion

Patients with BD in a euthymic state have PS compared with healthy controls, specifically a cognitive slowing related to generating a movement. In addition, a slowed motor component of movement was found when the cognitive load was high and only in the presence of residual depressive symptoms. This study provides valuable insight into the interaction between cognitive and motor slowing present in BD. The presence of cognitive slowing in euthymia indicates a state independent abnormality which may be related to the pathophysiology of the disorder. The presence of PS in BD is critically important because of the prognostic ramifications for the patients.

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Chapter 3

Systematic review of cognitive event related potentials in euthymic bipolar disorder

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Abstract

Cognitive deficits are critical features of bipolar disorder (BD), greatly impacting quality of life. The aim is to systematically review and critically evaluate underlying event related potential (ERP) features in euthymic BD relating to differences in sensory processes, attention, inhibition and conflict monitoring compared with healthy controls. 911 unique articles were identified using the PubMed database and 14 studies met the inclusion criteria. Individuals with BD in a euthymic state have reduced P50 sensory gating and reduced P100 amplitudes compared with healthy controls. Many studies demonstrated reduced P300 amplitudes and normal P300 latencies in BD. In addition, reduced NoGo N2 and abnormal NoGo P3 activity were observed in BD. Finally, there is some evidence of reduced error-related negativity amplitudes in BD. Importantly, ERP modulations vary with stimulus factors and clinical profile. The functional significance of these findings and clinical implications are discussed. ERP differences in BD arise at various stages of cognitive processing, specifically in early auditory and visual processing, attention allocation, context updating, inhibition and conflict monitoring. Treating these deficits and their underlying neurobiological disturbances corresponding to abnormal performance on cognitive tasks may aid functional remission. This knowledge might enable personalized treatment interventions targeting specific cognitive deficits.

Introduction

Bipolar disorder (BD) is a chronic psychiatric disorder characterized by recurring manic or hypomanic episodes and additional depressive episodes usually separated by periods of euthymic mood (APA 2013). Mood changes in BD are known to negatively impact cognitive performance, with evidence of cognitive abnormalities becoming more severe during manic and depressive episodes (Ferrier et al., 1999; Clark et al., 2002; Martinez-Aran et al., 2004). Disturbances in cognition affect social and occupational functioning of individuals (Green 2006; Malhi et al., 2007), with improvement in the quality of life and clinical symptoms associated with increased cognitive skills (Campanella 2013). Importantly, many neuro-cognitive abnormalities have been found to persist in euthymia, including difficulties with verbal memory, attention, executive functioning and psychomotor functioning (Arts et al., 2008; Bearden et al., 2001; Bora et al., 2009; Martinez-Aran et al., 2004). The presence of cognitive deficits during remission suggests that they are core symptoms of BD allowing for an investigation of abnormalities that may be related to the BD pathophysiology.

The identification of neural underpinnings relating to abnormal cognitive performance can be achieved through neuroimaging techniques such as fMRI, which has excellent spatial resolution (Turner and Jones 2003), allowing a broad identification of neural networks involved during specific tasks. Using fMRI in BD, differences amongst individuals in an elevated mood state compared to those in a euthymic state have been identified (see Kupferschmidt et al., 2011 for review). For example, hypo-activation of the dorsal attention network was demonstrated in euthymia compared with hyper-activation in mania (Brady et al., 2017). Persistent cognitive deficits in euthymia together with different neuronal patterns to symptomatic BD highlight the importance of identifying neurophysiological underpinnings in euthymic BD, as these may further our understanding of the

pathophysiology of the disorder and have important implications for treatment strategies helping to achieve greater rehabilitation.

Unfortunately, brain activations using fMRI are averaged over seconds and are too slow to determine which specific brain activation is related to each cognitive stage involved in a task (Turner and Jones 2003). However, once cortical abnormalities have been identified via fMRI, more specific inferences can be made using electrophysiology on these components (Michel and Murray 2011). Electrophysiology, specifically cognitive event related potentials (ERP), has the advantage of high temporal resolution (averaged over milliseconds), allowing different electrophysiological components to be observed, each representing distinct cognitive stages occurring during a task (Nunez 1981). ERP components may be considered biological markers of the disorder provided their features enable a distinction between BD and other disorders, indexing specific pathophysiological mechanisms that may or may not recover with illness remission.

In BD, ERP studies have mainly focused on early sensory processing, attention, inhibition and conflict monitoring in order to identify underpinnings related to the cognitive and behavioral deficits present in BD. The P50 is a positive component appearing 50 msec after stimulus presentation and reflects an early process of auditory perception (Picton, 1974). An early process of visual perception is reflected in the P100 which is elicited in response to visual stimuli and has a positive waveform occurring between 50-150 msec following stimulus onset (Desmedt et al., 1983). Other ERP components reflecting early sensory processing include the N100 and P200, a negative ERP component followed by a positive component, appearing 50-150 msec and 200 msec following stimulus onset respectively (Näätänen and Picton 1987). Tasks involving attention have been found to elicit the N200, a negative ERP deflection occurring 200-350 msec following stimulus presentation (Folstein and Van Petten 2008). The N200 is followed by a positive waveform P300 appearing 250-500 msec following stimulus onset which is elicited in response to the detection of rare or novel target stimuli amongst frequent stimuli, with amplitudes reflecting

context and memory updating (Donchin and Coles 1988; Polich 2004) and latencies thought to reflect information processing speed (Duncan-Johnson and Donchin, 1977; Leuthold and Sommer, 1999). The NoGo N2 and NoGo P3 are two components reflecting inhibitory control (De Jong et al., 1990; Jonkman et al., 2003; Smith et al., 2006; Kok et al., 2004). The NoGo N2 is associated with conflict detection during early stages of the inhibition process (Nieuwenhuis et al., 2003) and the NoGo P3 reflects inhibition of the motor system (Kok et al., 2004). The ERN is a negative going component appearing 100-150 msec after an erroneous response, signifying the detection of an error or conflict between intended and actual response (Gehring et al., 1993; Falkenstein et al., 1990) and reflects conflict monitoring in the brain. This is followed by the Pe, a positive component occurring 150-400 msec following an error (Falkenstein et al., 2000; Van Veen and Carter, 2002; Nieuwenhuis et al., 2001) and reflecting error awareness (Dhar et al., 2011; Endrass et al., 2012).

In an attempt to synthesize the findings in BD, a recent review of neurophysiological findings in BD was conducted (Onitsuka et al., 2013). Unfortunately, data specifically relating to ERP in euthymic BD was limited to two studies, with one discussing early sensory processing and the other attention (Sanchez-Morla et al., 2008; Fridberg et al., 2009). This underrepresentation of the data was likely due to the nature of the review. The authors included studies using a broad range of neurophysiological techniques including evoked and event related potentials, neural oscillation and synchronization and near-infrared spectroscopy studies, with the intention of reporting a general overview of major neurophysiolgical findings in BD (not specific to euthymia), rather than a systematic review of all ERP findings in BD. In addition, a number of studies have been conducted since 2013, warranting an updated review.

The interpretation of ERP findings is complicated by a number of confounding effects. Although individuals with BD in a euthymic state are clinically stable, the presence of low-level residual mood symptoms is common (Martinez-Aran et al., 2004). Elevated mood influences cognitive performance, which is reflected in ERP

activity as well (Elliott 1998; Morsel et al., 2014; Kaya et al., 2007). In addition to residual symptoms affecting cognition and ERPs in euthymia, a lifetime history of psychosis (prevalent in 58% of BD I, see Goodwin 2007) seems to be responsible for poorer performance on neuro-cognitive tasks (Tabares-Seisdedos et al., 2003; Simonsen et al., 2009) and a greater number of ERP abnormalities (Olincy and Martin 2005; Lijffijt et al., 2009). A third potential confounding factor in the interpretation of ERP activity in BD is the influence of medication. Although it is unclear in which way medications impacts cognition and ERP, findings are limited with some studies demonstrating a decline in cognitive performance when taking antipsychotics and some evidence of lithium and antipsychotics enhancing cognition (Daglas et al., 2016; Yatham et al., 2017). In addition, while some studies did not demonstrate any influence of medication on ERP (Strik et la., 1998; O'Donnell et al., 2004) there is evidence of reduced ERP amplitudes in individuals taking benzodiazepines (de Bruijn et al., 2006), and further evidence of increased amplitudes in individuals taking lithium compared with those taking antipsychotics (Small et al., 1998).

The aim of the current article is to systematically review and evaluate visual and auditory ERP literature in euthymic BD compared with healthy controls. Studies investigating ERP components related to early sensory processing, attention, inhibition and conflict monitoring, are discussed. As ERP amplitudes and/or latencies may be modulated by residual mood, history of psychosis and medication, thereby confounding results, these factors are specifically examined in the reviewed articles. In addition, this review provides a critical discussion of limitations in the empirical literature as a guide for future investigations.

Methods

Search strategy and selection criteria

A systematic literature search was performed and article selection was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Figure 1 illustrates a flowchart of the study selection process. MEDLINE (via PubMed database) was searched in January 2018 using the search terms (bipolar disorder) AND ((ERP) OR (EEG) OR (event related potentials)) and the search was restricted to articles written in English. The search identified a total of 911 unique articles.

Articles were retained if they investigated neuro-cognitive processing and measured an ERP component in BD. Articles were included if they related to sensory processing, attention, inhibition or conflict monitoring and provided a statistical analysis of a comparison with healthy controls. In addition, studies were included if they used a sample of adults with BD who were in a euthymic state. Report of ERP component amplitudes or latencies was essential for inclusion.

Studies were excluded from the review if ERP measures were used to investigate any other processes other than cognitive impairment (i.e. sleep) or cognitive processes not specified in the aims of the review (for example, social cognition and decision making). Non-human studies were excluded as were studies that did not test adults. Case studies and reviews were also excluded.

All titles and abstracts were screened (by A.M.) to exclude any irrelevant studies. A total of 182 articles remained and these full text articles were read to determine if they met the inclusion and exclusion criteria. In total, 14 studies met the search criteria and were reviewed in this paper. The following data was obtained from each of the selected studies: participant group and sample size, cognitive process, ERP component measured, topographical location, stimulus modality, task

used, ERP amplitude and/or latency findings, relationship to mood, history of psychosis and medication.

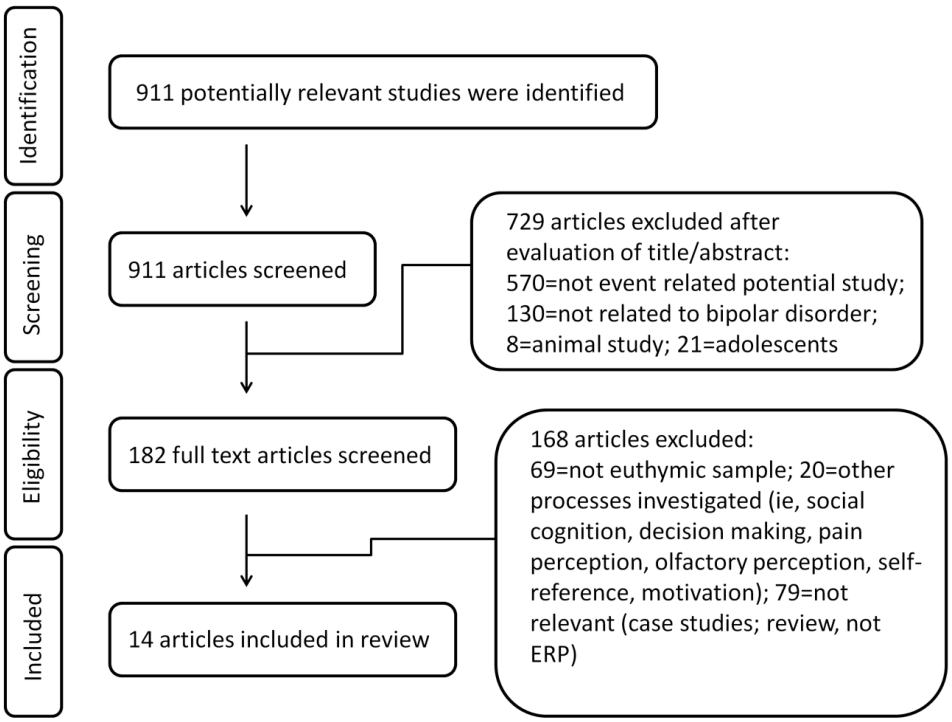

Figure 1: Flow chart illustrating the steps taken in study selection

Results and Discussion

Fourteen articles met the inclusion criteria. Table 1 presents an overview of task details and main findings of the studies reviewed and Table 2 presents an overview of demographic and clinical data of the samples investigated in each study. Amongst these 14 articles, a number of studies investigated ERPs relating to more than one cognitive process with 7 studies relating to sensory processing, 9 relating to

attention, 3 studies relating to inhibition and 2 relating to conflict monitoring. Results are reviewed and discussed according to the cognitive process under investigation.

Early sensory processing

In the auditory modality, an indication of pre-attentive sensory processing can be seen as a positive peak occurring about 50 msec after the presentation of the stimulus, referred to as the P50, and is located at frontocentral regions of the scalp (Picton 1974). In terms of the stages of information processing, this component represents an early process of perception and is referred to as an 'exogenous' ERP component as it depends largely on the physical features of the stimulus. Paradigms used to elicit the P50 often use auditory clicks. In addition to P50 assessing early sensory processing, a second repetitive auditory stimulus (about 500 msec later), has been found to evoke a suppression of P50 waveforms compared with the first stimulus. A comparison of the amplitudes of the first conditioning stimulus (S1) and the second test stimulus (S2) (via their ratio or difference) can be used to measure sensory gating, a more complex stage of pre-attentional information processing. Sensory gating refers to habituation of repetitive input and requires an inhibitory response to the repetitive (or irrelevant) stimuli (Adler et al., 1982). The ability to block out irrelevant stimuli is critically important in navigating our sensory filled environment.

In the visual modality, the early exogenous ERP component P100 can be seen as a positive peak occurring about 50-150 msec after the presentation of a visual stimulus and is located at the occipital cortex.

Two other ERPs at an early stage of information processing are elicited following stimulus presentation regardless of stimulus modality; the negative peak N100 and positive peak P200. The N100/P200 components are interrelated and may reflect the convergence of sensory information (Näätänen and Picton 1987). In terms of the stages of information processing, these components may represent an

integrative process of perception and attention and are referred to as mesogenous components (Picton and Stuss 1980). N100 occurs between 80 and 120 milliseconds following stimulus onset and is distributed over the fronto-central region of the scalp. It is elicited even in the absence of task demands and is larger when stimuli are new compared with repetitive or expected stimuli. The N100 is often followed by the P200 ERP which peaks approximately 200 milliseconds after stimulus presentation and is distributed over the fronto-central and parieto-occipital regions of the brain**.** Evidence that the P50 does not always correlate with the N100 or P200 (Lijffijt et al., 2009) suggests that they represent different underlying mechanisms and may be differently affected in BD.

Main findings

Two studies investigated auditory sensory gating in euthymic BD (Sánchez-Morla et al., 2008; Cabranes et al., 2013). A higher ratio of S2/S1 P50 amplitudes in BD was demonstrated reflecting reduced sensory gating compared with healthy controls. Cabranes and colleagues (Cabranes et al., 2013) additionally demonstrated deficits in S1-S2 difference gating which has been suggested to be more reliable than ratio gating (Dalecki et al., 2011). This implies that individuals with BD in a euthymic state have difficulties in the auditory modality inhibiting irrelevant pre-attentive sensory input. In addition, reduced P100 amplitudes were demonstrated in euthymic BD (Yeap et al., 2009) representing a dysfunction in early visual processing as well.

Individuals with BD in a euthymic state were found to have normal N100 amplitudes both in the auditory modality (Muir et al., 1991; Fridberg et al., 2009) and the visual modality (Bestelmeyer et al., 2012; Morsel et al., 2014). However, with respect to latency there is evidence of later N100s in euthymic BD (Muir et al., 1991) which reflects a disturbance of N100 timing. Early auditory processing in euthymic BD reflected by the P200 remains unclear with one study observing reduced P200

amplitudes (Fridberg et al., 2009) and another study demonstrating normal P200 amplitudes (Muir et al., 1991). It is possible that these reported differences may have been caused by differences in the BD subgroups tested (as Muir and colleagues (Muir et al., 1991) included some individuals with BD II).

There is no research on visual P200 in euthymic BD. However, in general there is little research on this component.

Clinical and medication influences

Reduced sensory gating was not related to residual mood symptoms in euthymia (Cabranes et al., 2013). Two studies compared individuals with BD in a euthymic state to those in symptomatic states and did not find different N100 or P200 activity amongst the groups (Muir et al., 1999; Fridberg et al., 2009). Similarly, N100 amplitudes were not affected by residual mood symptoms (Morsel et al., 2014).

Taken together these findings suggest that mood symptoms, even mild residual symptoms, do not seem to influence these early ERP components. These findings extend results from a number of studies that investigated individuals with BD in manic and depressed states and did not find that reduced gating in BD was influenced by either manic or depressed symptoms (Lijffijt et al., 2009; Olincy and Martin et al., 2005; Schulze et al., 2007). Similarly, one study, investigating individuals with BD in manic and mixed mood states demonstrated comparable N100 and P200 amplitudes to healthy controls, suggesting that these components were not influenced by mood symptoms (O'Donnell et al., 2004).

Reduced sensory gating was demonstrated in euthymic BD with a history of psychosis (Sánchez-Morla et al., 2008) while those without a history of psychotic symptoms had normal sensory gating (Sánchez-Morla et al., 2008) or less significant reduction of gating (Cabranes et al., 2013). The influence of having a history of

psychosis on P100 activity was not investigated (Yeap et al., 2009) and it did not appear to influence the N100 or P200 (Fridberg et al., 2009).

The suggestion that reduced gating in euthymia is related to a history of psychosis is in line with findings from studies that investigated individuals with BD in symptomatic states which also demonstrated that reduced gating is related to history of psychosis (Lijffijt et al., 2009; Olincy and Martin et al., 2005; Schulze et al., 2007). This suggestion is also in line with sensory gating abnormalities present in schizophrenia (see meta-analysis, Bramon et al., 2004). Schulze and colleagues (Schulze et al., 2007) suggested that reduced gating may underlie psychotic symptoms rather than be specific to BD. On the other hand, the findings of normal N100 amplitudes in euthymic BD are in contrast to the abundant evidence of reduced N100 in individuals with schizophrenia (see review, Onitsuka et al., 2013). O'Donnell and colleagues (O'Donnell et al., 2004) suggested that early sensory processing reflected by the N100 might differentiate these disorders and may be a biological index used to distinguish between BD and schizophrenia.

Medication (mood stabilizers, antidepressants, antipsychotics and benzodiazepines) did not appear to influence sensory gating (Sánchez-Morla et al., 2008; Cabranes et al., 2013), N100 or P200 activity in euthymia (Muir et al., 1991; Fridberg et al., 2009).

Attention

In addition to difficulties in early sensory processing, there is evidence that individuals with BD in a euthymic state have deficits in sustained attention (Dickerson et al., 2004). This has important clinical implications for daily functioning, possibly affecting job maintenance and treatment compliance. The most commonly investigated ERP component in BD in relation to attention is the P300 (see Maekawa et al., 2012). This component is thought to reflect context and memory updating and generally P300 amplitude increases with the amount of attention allocated to the

task (Donchin and Coles 1988; Polich 2004). P300 latencies on the other hand reflect information processing speed (Duncan-Johnson and Donchin, 1977; Leuthold and Sommer, 1999). In terms of the stages of information processing, these ERP components are 'later' stages requiring conscious attention and represent high-level cognitive processes. These more 'endogenous' components therefore reflect the cognitive demands of the task, irrespective of stimulus modality.

The P300 can be divided into two components, the novelty P3 (or P3a) and the classic P300 (or P3b) (Snyder and Hillyard 1976). The novelty P3 is elicited in response to orienting to novel events (independent of task relevance) (Kok 2001) and has a more frontal scalp distribution (Courchesne et al., 1975). The classic P300 is elicited in response to the detection of rare target stimuli presented amongst a train of frequent stimuli with a positive waveform occurring around 250-500 milliseconds after stimulus onset (Johnson, 1993), and is located at parietal regions of the scalp (Conroy and Polich 2007). Paradigms used to elicit the P300 often employ a traditional two-stimulus oddball paradigm, an attention task where subjects have to respond to infrequent target stimuli and not respond otherwise. In addition to the P300, attention tasks have been found to elicit an earlier component, the N200 which peaks around 200-350 msec after stimulus presentation and has been found to be generated at anterior sites (Folstein and Van Petten, 2008). The majority of studies investigating attention reflected by P300 activity in individuals with BD have used the auditory modality.

Main findings

The majority of studies investigating P300 in euthymic BD focused on P3b activity. While most studies found significantly reduced amplitudes in the auditory modality (Muir et al., 1991; Fridberg et al., 2009; Bestelmeyer et al., 2009; Bersani et al., 2015; Kaya et al., 2007), one study contradicted these findings and demonstrated comparable P3b amplitudes in euthymic bipolar disorder to healthy controls (Lahera

et al., 2009). In the visual modality, two studies demonstrated comparable P3b in euthymic BD to healthy controls (Bestelmeyer et al., 2009; Bestelmeyer et al., 2012), while one study observed reduced P3b amplitudes (Morsel et al., 2014).

Regarding latencies, the majority of studies (Fridberg et al., 2009; Bestelmeyer et al., 2012; Bestelmeyer et al., 2009; Bersani et al., 2015; Kaya et al., 2007) excluding one (Muir et al., 1991) demonstrated normal P3b latencies (auditory and visual) in euthymic BD compared with healthy controls. It is important to note that task details and ERP measurements in the study of Kaya and colleagues (Kaya et al., 2007) are unknown, therefore the results need to be interpreted with caution.

Results of the studies suggest that information processing speed in euthymic BD appears to be intact, and memory and/or attention seems to be compromised. However, the exact implication of reduced P300 amplitudes in BD is under debate. Some say that this indicates a limitation of available resources (Linden, 2005), while others argue that it reflects a dysfunction in the ability to allocate these resources effectively (Wickens et al., 1983).

In an investigation of the P3a component, one study demonstrated comparable amplitudes to controls (Bestelmeyer et al., 2012). Four studies have investigated the N200 component in euthymic BD and observed normal N200 activity (Muir et al., 1991; Fridberg et al., 2009; Morsel et al., 2014; Michelini et al., 2016).

Clinical and medication influences

It is possible that mood symptoms influence the ERP components relating to attention. In one study, individuals with BD in a euthymic state with residual depressive symptoms experienced larger P300 reduction (Kaya et al., 2007). On the other hand, a few studies comparing individuals with BD in a euthymic state to those in symptomatic states did not find any differences in N200 or P300 activity suggesting that mood state did not influence these ERP components (Muir et al., 1991; Fridberg et al., 2009)

Two studies compared individuals with BD in a euthymic state with a history of psychosis to those without (Fridberg et al., 2009; Lahera et al., 2009) and did not find any influence of having a history of psychosis on P300 activity. However, studies which directly compared individuals with BD in a euthymic state to healthy controls as well as individuals with schizophrenia found that the two psychotic disorders could not be differentiated based on P300 amplitudes and latencies (Muir et al., 1991; Bestelmeyer et al., 2009; 2012), suggesting that reduced P300 activity may be characteristic of all psychotic disorders rather than specific to individuals with BD. This is in line with the widely demonstrated findings of reduced P300 amplitudes in individuals with schizophrenia (see review Onitsuka et al., 2013).

It must be noted that reduced P300 amplitudes are seen in a wide range of disorders, for example depression, substance abuse, ADHD, PTSD (Roth 1981, Moeller et al., 2004; Verbaten et al., 1994; Metzger et al., 1997) and are not specific to psychotic disorders. However, the reasons behind reduced P300 amplitudes can be different. For example, amplitudes in the group average can be reduced because less attentional resources go into information processing. However, this may not be the case for all individuals and there may be great variability between individuals within the clinical spectrum. Likewise, another cause for reduced amplitudes in group comparisons can be high variability in latency within (trial-to-trial latency jitter) or between individuals of one group, which will lead to a reduction in amplitude in the group average. Furthermore, it is important to take topography into account, given that if an ERP component is more lateralized in one group, this will lead to artificially reduced amplitudes if the component is evaluated at single lead (e.g. P300 at Pz).

Unfortunately, only two studies investigating attention in euthymia using ERP investigated effects of medications (mood stabilizers, antipsychotics and antidepressants) and did not find any drug influence on N200 or P300 activity (Muir et al., 1991; Fridberg et al., 2009).

Inhibition

Behavioral deficits on neuropsychological tasks relating to inhibition are often demonstrated in BD. Difficulty to inhibit responses relates to impulsive behavior, a clinically observable phenomenon in BD and extreme manifestations of impulsivity impair everyday functioning and represent important targets for treatment interventions (Evenden, 1999; Moeller et al., 2001). Paradigms gauging inhibitory control, such as the Go/No-Go task, require subjects to respond to a visual stimulus on most trials and intermittently inhibit a prepotent response. On a neurophysiological level, an accurate reflection of inhibitory control is indexed by two distinct ERP components; the NoGo N2 and the NoGo P3 (De Jong et al., 1990; Jonkman et al., 2003; Smith et al., 2006; Kok et al., 2004). The NoGo N2 is associated with conflict detection during early stages of the inhibition process (Nieuwenhuis et al., 2003) and has been proposed to be generated in the anterior cingulate cortex (ACC) and inferior cingulate cortex (Lavric et al., 2004). The NoGo P3 is a later component reflecting actual inhibition of the motor system (Kok et al., 2004). Both the NoGo N2 and the NoGo P3 have been shown to be most robust at fronto-central areas when responses have to be inhibited (Bokura et al., 2001; Fallgatter et al.,1997; Tekok-Kilic et al., 2001).

Main findings

Three studies have investigated ERPs relating to inhibition in euthymic BD, and findings remain inconclusive. One study, using a three stimulus oddball task that included elements of inhibition (subjects had to inhibit responses to a novel stimulus) and attention (P3b), demonstrated normal NoGo P3 amplitudes in euthymia (Bestelmeyer et al., 2012). This finding is in contrast to two other studies. One study (using a cued continuous performance test) demonstrated reduced NoGo N2 together with reduced NoGo P3 in euthymic bipolar disorder (Michelini et al., 2016)

suggesting an overall aberrant inhibition process in BD. Another study using a Go/No-Go paradigm demonstrated marginally reduced NoGo N2 and *increased* NoGo P3 using a very simple task (Morsel et al., 2017), suggesting that individuals with BD have difficulties in an early stage of conflict detection, but compensate for these difficulties at a later stage of the inhibition processes leading to normal performance.

These results may be related to methodological differences amongst the studies. While the NoGo P3 has been found to be more robust at fronto-central electrodes during inhibition (Bokura et al., 2001; Fallgatter et al., 1997; Tekok-Kilic et al., 2001), Bestelmeyer and colleagues (Bestelmeyer et al., 2012) focused their investigation at parietal sites, which may be the cause of the contradictory results. In addition, the tasks used in the studies varied in complexity possibly suggesting that when task demands are higher, individuals with BD are no longer able to compensate successfully, and this leads to reduced NoGo P3 and aberrant inhibition.

Clinical and medication influences

There was some evidence that symptom severity, specifically residual depression was related to reduced NoGo N2 activity, in line with evidence of a hypersensitivity to incorrectly responding in BD (Morsel et al., 2017). More research needs to be carried out to confirm effects of residual symptoms on ERP activity relating to inhibition in euthymic BD, especially residual manic symptoms as mania clearly exasperates impulsivity (Larson et al., 2005). It is important to note that in the study of Michelini (Michelini et al., 2016) only women were included. While there is no indication of gender differences in electrophysiological measures in BD, these results may not be representative of all individuals with BD. Unfortunately, the studies did not control for history of psychotic symptoms, which may influence the ERP components relating to inhibition just as it may influence the P50 and P300.

Medications, specifically benzodiazepines, were found to reduce the NoGo P3 (Morsel et al, 2017) and when effects of medications were controlled for,

individuals with BD in a euthymic state demonstrated increased NoGo P3 activity. Thus, medications may have been the underlying cause of reduced NoGo P3 found in the study of Michelini and colleagues (Michelini et al., 2016).

Conflict monitoring

Conflict monitoring is a cognitive control process of continuously evaluating ones performance and making subsequent behavioral adjustments to fit changing environmental demands. When an error is detected, it is important to correct performance. Abnormal error detection would result in a lack of monitoring performance and thereby result in seemingly impulsive behavior, a clinically observable phenomenon in BD (Najt et al., 2007). Conflict monitoring therefore has important implications for daily life functioning (Ullsperger, 2006).

The error-related negativity (ERN) also referred to as the error negativity (Ne) is thought to reflect error detection, an important aspect of conflict monitoring (Gehring et al., 1993; Falkenstein et al., 1990). The ERN manifests as a negative deflection in the ERP waveform that peaks 50-150 msec after error commission. Localization studies and fMRI imaging studies have shown that the ERN is generated in the anterior cingulate cortex (ACC) (Gehring et al., 1993; Dehaene et al., 1994) and is maximal at fronto-central electrodes (Gehring et al., 1995). The ERN is followed by a positive deflection known as the error positivity (Pe) which peaks 150-400 msec after an error is made (Falkenstein et al., 2000; Van Veen and Carter, 2002; Nieuwenhuis et al., 2001). Neural generators of the Pe have been localized in the ACC and insula (Dhar et al., 2011; Ullsperger et al., 2010) with maxima at central-parietal electrodes. As the Pe is enhanced when there is an awareness of errors, this component has been proposed to reflect conscious error perception (Falkenstein et al., 2000) and is triggered by the salience of errors (Dhar et al., 2011; Endrass et al., 2012).

Main findings

While conflict monitoring using ERP measures has been extensively investigated in many major psychiatric disorders such as schizophrenia, depression and anxiety disorders (see Olvet and Hajcak 2008 for review), there is relatively little evidence regarding ERN (Morsel et al., 2014; Kopf et al., 2015) and Pe (Kopf et al., 2015) in euthymic BD. Using a flankers task, reduced ERN amplitudes (Morsel et al, 2014; Kopf et al., 2015) and normal Pe (Kopf et al., 2015) were found in BD subjects compared with healthy controls, demonstrating that individuals with BD in a euthymic state have difficulties detecting errors, an important aspect of conflict monitoring.

Clinical and medication influences

Depressive symptoms were associated with increased ERN amplitudes. This was observed amongst individuals in a euthymic state who had residual depressive symptoms (Morsel et al., 2014) and amongst individuals with BD in a depressed state (Kopf et al., 2015). These findings are in line with evidence of increased ERN amplitudes in depression, which is indicative of hypersensitivity to errors in depression (Olvet and Hajcak 2008). Thus, there are likely additional state related influences on the ERN in addition to trait related ERN abnormalities.

One study observed that individuals with BD in a euthymic state with a history of psychosis did not have different ERN amplitudes compared with those without a history of psychosis (Morsel et al., 2014). Effects of medication do not appear to influence the ERN (Morsel et al., 2014; Kopf et al., 2015; Minzenberg et al., 2014).

Limitations

It is important to consider the limitations of the studies reviewed. These include methodological and publication biases, confounding variables that may have influenced ERP activity (such as bipolar subgroup and co-morbidities) and different aspects that make comparing studies difficult (such as employing different clinical profiles across studies or task differences). These limitations will be further discussed.

Firstly, there may be methodological bias amongst the studies, as unfortunately many employed very small sample sizes. Although it is not known if they are statistically underpowered (as none of the studies gave details as to how sample size was derived), underpowerment is very likely, as is the case in many neuroscience studies (Button et al., 2013). This leads to a high probability of random error with either a low chance of discovering effects or magnified effect sizes (Button et al., 2013). As such, many differences amongst the studies may be a result of this bias. It is also hard to generalize results from small studies. In addition, there may be a publication bias with published papers mostly reporting positive results. Unfortunately, it is difficult to access unpublished papers and assess all results found, highlighting the great responsibility of researchers and journals to publish papers with null results in order to limit this bias.

Cognitive disturbances may be less severe in individuals with BD II compared with BD I, (Torrent et al., 2006), however, most studies did not take BD subgroup into account while analyzing ERP relating to cognitive disturbances in euthymia. Most studies investigated ERP in BD I or in mixed samples. However a few studies used separate BD I and BD II samples and did not find differences in ERP activity relating to sensory gating (Cabranes et al., 2013), P100 activity (including only 3 individuals with BD II: Yeap et al., 2009), N100 /P200 amplitudes (Muir et al., 1999) or P300 amplitudes (Muir et al., 1999; Bersani et al., 2015). In other words, although

cognitive disturbances may be less severe in BD II, there is no neurophysiological evidence for differences in ERP activity between these subgroups.

In addition, co-morbidities such as substance abuse in BD are common (with some reports of more than 50%, see Cassidy et al., 2001) and the effects have not been adequately addressed. Only one study controlled for the effects of substance abuse (Fridberg et al., 2009) and did not find any effects of substance abuse on P300 activity. While many of studies excluded individuals with substance abuse in order to exclude possible influences on the interpretation of ERP, it is important for future studies to take co-morbidities, specifically substance abuse, into consideration as cognitive abnormalities and subsequent underlying ERP components may be influenced by this factor. For example, alcohol in low and moderate quantities affects ERN amplitudes (Easdon et al. 2005).

Individuals with different clinical profiles were included in most studies. This includes those with a history of psychosis and those without, those with residual symptoms, differences in illness duration and number of episodes. These factors may all influence both cognitive and ERP results and variability of controlling for these clinical factors across studies makes it difficult to directly compare results across studies. Presenting the data as a meta-analysis would have many benefits in quantifying the results, allowing an exploration of effects of different clinical factors and co-morbidities on ERP activity. Unfortunately, to date, there are too few studies investigating many ERP components in euthymia for a meaningful meta-analysis to be conducted. For example, only one sample of individuals with BD in a euthymic state has been used to investigate sensory gating and only two studies were conducted investigating ERN reflecting conflict monitoring (Morsel et al., 2014, Kopf et al., 2015).

In addition to variability across subjects, the studies included employed different tasks, different variations/complexities of the tasks, different stimulus modalities and topographical locations. For example, in the investigation of P3b, both visual and auditory oddball tasks were conducted. Two studies required participants

to count the oddballs while other studies required a button press. These differences add to the complexities in comparing results. The majority of studies investigating ERP in BD did not control for effects of medication. It is unclear how medication impact EEG; for example, there is some evidence that antipsychotics (haloperidol and olanzapine) and benzodiazepines reduce the ERN (De Bruijn et al., 2004; 2006). Therefore, the interpretation of ERPs may be complicated by medication effects. The numerous methodological differences amongst the studies make comparisons difficult and hamper interpretations of the results.

It must be noted that the subject samples used in the two investigations of sensory gating in euthymic BD (Sanchez-Morla et al., 2008; Cabranes et al., 2013) overlapped. Each study had a different aim; one was to compare BD with and without a history of psychosis with schizophrenia, and the other study aimed to compare BD I and BD II with healthy controls. It is not surprising that both studies demonstrated abnormal gating in euthymic BD. More studies are needed to confirm these results. Similarly, two studies (Bestelmeyer et al 2009; 2012) using different tasks and with different aims used the same sample of individuals with BD. Thus, there is less evidence of reduced P300 amplitudes than it appears.

Summary of main ERP findings in euthymic BD

Early studies investigated ERP components related to attention and early sensory processing. Abnormal sensory gating was found in euthymic BD, reflecting a difficulty in inhibiting irrelevant pre-attentive stimuli. Gating abnormalities in BD may be dependent on a history of psychosis. Reduced P300 amplitudes reflecting context and memory updating are also commonly observed in euthymic BD, and may be related to all psychotic disorders, not specifically BD. More recently there has been a shift in focus and studies have investigated ERP components relating to the executive control processes of inhibition and conflict monitoring. Individuals with BD in a euthymic state demonstrated abnormal NoGo P3 activity relating to inhibition during

an easy task. Lastly, reduced ERN amplitudes were demonstrated in euthymia reflecting difficulties detecting errors, an important aspect of conflict monitoring.

Identifying these ERP abnormalities that underlie cognitive abnormalities in euthymia suggest that these deficits may be related to the BD pathophysiology. This review highlights the numerous methodological differences across studies (such as using different clinical samples, tasks, and controlling for different confounding factors). It is important for future studies to take additional factors such as residual mood symptoms, history of psychosis and medication into account in order to compare different studies and integrate findings.

Conclusions

Until recently the negative effects of cognitive dysfunction on psychosocial functioning were largely underestimated in individuals with BD in a euthymic state (Martinez-Aran et al., 2007). Clearly, individuals in remission continue to have very severe psychosocial difficulties due to cognitive deficits. Using electrophysiological measures in conjunction with cognitive tasks in BD enables direct measurement of brain activity during various stages of cognitive processing. Using this approach may largely increase our knowledge of underlying neurobiology relating to clinical symptoms in the hope of better treatment management. Abnormal ERP activity has been detected during various stages of information processing in euthymic BD, beginning with very early stages of sensory processing all the way to abnormalities in later cognitive processes.

In order to pinpoint underlying abnormalities, it is critically important to take into account any cascading effects of disrupted processing. For example, difficulties at very early stages (such as the inability to inhibit irrelevant pre-attentive sensory input) may lead to sensory overload and may underlie other abnormalities known to be present in BD such as aberrant attention (Dickerson et al., 2004). In fact, there is evidence of a direct relationship between reduced P50 gating and attentional

difficulties in individuals with schizophrenia (Cullum et al., 1993; Guterman et al., 1994). Abnormal P50 gating may therefore underlie reduced P300 amplitudes in BD; however this inference needs to be made with caution as P50 and P300 have different topographical locations (namely fronto-central and parietal respectively) and most studies focused their analyses on one specific location making comparisons difficult. Interestingly, difficulties in early pre-attentive sensory processing do not appear to influence information processing speed in BD (as normal P300 latencies have been observed).

Clinical implications

Evidence demonstrating difficulties during different levels of the information processing stream which are independent of one another has large implications for treatment. The knowledge gained from ERP studies of whether behavioral problems are perceptive, related to attention, inhibition or response related might enable personalized treatment interventions targeting specific cognitive deficits using 'ERP-oriented cognitive rehabilitation' in combination with medication and psychotherapy (Campanella et al., 2013) in order to improve the overall functional outcome of the individuals. ERP-informed cognitive rehabilitation can include an important interventional strategy of neuromodulation by brain stimulation using techniques such as repetitive Transcranial Magnetic Stimulation (rTMS) or transcranial direct current stimulation (tDCS). These non-invasive treatments stimulate brain tissue to induce currents which may normalize activity and have demonstrated cognitive improvement in individuals with psychiatric disorders (Guse et al 2010; Martis et al., 2003) and in healthy subjects (Mottaghy et al 1999; Boroojedi et al., 2001). Importantly, there is evidence of increased P300 amplitudes in euthymic BD following tDCS (Bersani et al., 2015).

In addition to ERP-guided treatment development and cognitive remediation, the clinical application of ERP may also have potential to increase diagnostic accuracy

in terms of various stages of cognitive processing. For example, differences in N100 amplitudes may distinguish BD from schizophrenia, and normal P300 latencies demonstrated in BD (for example, Fridberg et al., 2009; Bersani et al., 2015) may be distinguished from commonly reported longer P300 latencies in unipolar MDD (see Olbrich and Arns 2013 for review of EEG in MDD). Further research is needed to investigate diagnostic utility and accuracy.

Future developments

Future research should focus on investigating the specificity of ERP abnormalities relating to cognitive processes occurring at later stages and their relationship to information processes occurring at earlier stages. For example, the relationship between P3b and P50 should be further investigated.

In addition, the specificity of ERP abnormalities to BD remains unclear. More studies are needed directly comparing individuals with BD in a euthymic state to those with other major psychiatric disorders such as schizophrenia and MDD.

It is also essential for future investigations to control for clinical differences, specifically residual mood and psychoses as these clearly modulate the ERP. While it is extremely difficult to control for effects of medication as all individuals with BD are on a wide range of medications, once ERP abnormalities have been identified, it may be beneficial to compare ERP activity in BD while taking different medications. As more ERP studies in euthymic BD are generated, it would be beneficial to conduct a meta-analysis allowing an exploration of effects of clinical variables, such as gender distribution, average age, medication, co-morbidity, history of psychosis, bipolar disorder type and residual mood symptoms. Including studies investigating individuals with BD in all mood states would additionally allow an exploration of the effects of mood episodes on the ERP.

Crucially, in BD the focus has been on information processing in the absence of emotionally salient contexts. There is still much to be learned from investigating

information processing of emotional information or of neutral information within an emotional context (Malhi et al., 2005) in order to investigate the interaction between cognitive and emotional processing (Bush et al., 2000), which may in fact underlie differences at even the earliest stages of cognitive processing.

Table 1: Overview of task details and main findings of ERP studies in euthymic BD

Study	ERP investigated	Topographical location	Task	Modality	Frequent: infrequent stimulus ratio	ERP detection	Randomization	Feedback	Main finding
Bersani et al. (2015)	P3b	Fz, Cz, Pz	oddball task	auditory	4:01	largest peak + mean voltage	randomly presented	No	<P3b amplitudes in BD compared with control, normal P3b latency. BDI=BD II
Bestelmeyer et al. (2009)	P3b	FCz, Cz, Pz	oddball task	auditory and visual	4:01	largest peak	pseudo-randomized; each oddball trial followed by at least 3 standard stimuli	No	<P3b amplitudes in BD compared with controls (significant for auditory; a trend for visual)
Bestelmeyer et al. (2012)	N100, P3a, P3b	FCz, Cz, Pz	three-stimulus oddball task	visual	4:1:1 (infrequent =target oddball and meaningless distractor)	largest peak	pseudo-randomized; each target or distractor trial followed by at least 3 standard stimuli	No	BD = controls for P3a and P3b amplitudes; BD also = schizophrenia (who had <P3a, P3b amplitudes compared with controls)

Cabranes et al. (2013)	P50 sensory gating; S2/S1 ratio, S1-S2	N/A	paired click paradigm	auditory	N/A	largest peak	N/A	No	<P50 sensory gating in BD. BD I=BD II
Fridberg et al. (2009)	N100, N200 -- P200 -- P3b	Fz -- Cz -- Pz	oddball task	auditory	17:03	mean voltage	randomly presented	No	Euthymic BD =N100 amplitudes; <P200 amplitude, = N200 amplitude; <P300 amplitudes and longer latencies compared with controls
Kaya et al. (2007)	P3b	N/A	oddball task	auditory	N/A	N/A	N/A	No	<P3b amplitudes in BD previously depressed patients; = P3b latency in both groups. Residual mood influences P300
Kopf et al. (2015)	ERN -- Pe	Fcz, Cz -- Cz,Pz	Eriksen flankers task	Visual	1:01	largest peak	randomly presented	visual feedback (emotional or neutral); late, error or correct	<ERN and =Pe in BD euthymia compared with controls (for errors)

Lahera et al. (2009)	P3b	Pz	oddball task	auditory	4:01	largest peak	randomly presented	No	BD=controls for P3b amplitudes and latency
Michelini et al. (2016)	NoGo N2, NoGo P3	Fz,Cz	cued CPT	Visual	1:01	mean voltage	pseudo-randomization; cue-Go or cue-NoGo	No	<NoGo N2 amplitude, <NoGo P3 amplitude in BD compared with controls
Morsel et al. (2014)	ERN,N1,N2 -- P3b	FCz -- Pz	Eriksen flankers task	Visual	1:01	largest peak	randomly presented	visual feedback; late, error or correct	<ERN amplitude in BD compared with controls
Morsel et al. (2017)	NoGo N2, NoGo P3	FCz, Cz	Go/NoGo task	Visual	7:03	largest peak	pseudo-randomized, each NoGo trial followed by at least 3 Go stimuli	No	marginally reduced NoGo N2 amplitudes , <NoGo P3 amplitudes in BD compared with controls
Muir et al. (1991)	P3b, N100, P200, N200	Cz	oddball task	auditory	9:01	largest peak	randomly presented	No	<P3 amplitude, <P3 latency in BD compared with controls
Sanchez-Morla et al. (2008)	P50 sensory gating S2/S1 ratio and S2	Cz	paired click paradigm	auditory	N/A	largest peak	N/A	No	< P50 gating in BD; specifically with history of psychosis

Yeap et al. (2009)	P1	occipital and parietal	Go/NoGo task	Visual	1:01	mean voltage	randomly presented	No	<P1 amplitude in BD

Table 2: Overview of demographic and clinical variables of the samples investigated in ERP studies in euthymic BD

Study	Participants	Gender (%Male)	Mean age (SD)	BD subtype	History of psychosis
Bersani et al. (2015)	10 BD euthymic 10 control	BD: 40% control: 40%	BD I: 47.2 (8.9) BD II: 48.5 (14.3) control: 46.2 (13.1)	10 BD I 10 BDII	N/A
Bestelmeyer et al. (2009)	19 BD euthymic 21 schizophrenia 35 control	BD: 37% Control: 46%	BD: 49.2 (10.6) control: 37.4 (11.9)	all BD I	N/A
Bestelmeyer et al., (2012)	19 BD euthymic 21 schizophrenia 19 control	BD: 37% Control: 46%	BD: 49.2 (10.6) control: 37.4 (11.9)	all BD I	N/A
Cabranes et al. (2013)	126 BD euthymic 95 control	BD: 44%, control: 48%	BDI: 43.5 BD II: 45.8 control: 42.4	100 BDI 26 BDII	81 BD I history of psychosis 19 BD I no history of psychosis
Fridberg et al. (2009)	62 BD euthymic 49 BD symptomatic 52 control	BD: 40% Control:46%	BD: 42.7 (12.8) control: 40.7 (11.6)	all BD I	8 history of psychosis 54 no history of psychosis/unknown

Kaya et al. (2007)	23 BD euthymic (previous episode manic) 20 BD euthymic (previous episode depressive) 22 control	BD: 56%, control 63%	BD last episode mania:36.6 (13.2) BD last episode derpession:40 (14) control: 35.5 (8.1)	all BD I	N/A
Kopf et al. (2015)	20 BD depressive episode 9 followed up when euthymic 20 control	BD whole sample: 55% control: 33%	BD: 44.3 (9.5) control: 44.2 (11.9)	9 BD I 11 BD II (not clear which ones were euthymic)	N/A
Lahera et al. (2009)	24 BD euthymic 38 control	BD: 41%, Control: 62%	BD: 43.9 (11.5), control: 48.9 (13.2)	all BD I	14 history of psychosis 10 no history of psychosis
Michelini et al. (2016)	20 BD euthymic 20 ADHD 20 control	All female	BD: 40.3 (7.7), control: 36.7 (4.3)	all BD I	N/A
Morsel et al. (2014)	16 BD euthymic 14 control	BD: 55%, control: 42%	BD: 46.9(10.8), control: 41.7 (14.6)	all BD I	N/A
Morsel et al. (2017)	20 BD euthymic 18 control	BD: 50%, control: 40%	BD:44 (12.1) control: 42 (15.1)	all BD I	N/A

Muir et al. (1991)	20 BD euthymic 14 BD depressed 24 BD manic 96 schizophrenia 46 MDD 213 control	BD whole sample: 61% control: 58%	BD: 35.2 (12.0) control: 30.5 (11.7)	75 BDI 13 BD II	N/A
Sanchez-Morla et al. (2008)	81 BD euthymic 92 schizophrenia 67 control	BD history of psychosis: 43%, BD no history of psychosis: 43% control: 66%	BD with history of psychosis: 44.7 (11), BD no history of psychosis: 46.6 (12) control: 43.8 (11.2)	No mention	51 psychosis 30 no psychosis
Yeap et al. (2009)	12 BD euthymic 12 control	BD: 50%, control: 58%	BD: 47.8 (12), control: 46 (12.7)	9 BD I 3 BD II	N/A

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Chapter 4

Inhibitory control in euthymic bipolar disorder: event related potentials during a Go/NoGo task

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Abstract

Objectives Patients with bipolar disorder (BD) are reported to have difficulties with inhibition, even in a euthymic state. However, the literature on cortical activity associated with response inhibition in BD remains ambiguous. This study investigates inhibition in euthymic BD using electrophysiological measures, while controlling for effects of specific medications.

Methods Twenty patients with BD were compared with eighteen healthy controls on a Go/NoGo task while electroencephalogram was recorded. Behavioral and event-related potential (ERP) measurements were analyzed for the two groups. Medication effects were controlled for in the analysis.

Results Patients with BD had marginally reduced NoGo N2 amplitudes and increased NoGo P3 amplitudes compared with healthy controls when patients using benzodiazepines were excluded from the study. No behavioural differences between the groups were found.

Conclusions Reduced NoGo N2 amplitudes in BD reflect aberrant conflict detection, an early stage of the inhibition process. In addition, increased NoGo P3 amplitudes in BD despite normal task performance reflect an overactive cortical system during a simple inhibition task.

Significance Difficulties in early stages of inhibition in BD appear to have been compensated by increased cortical activation. This study extends current knowledge regarding cortical activations relating to inhibition in BD.

Introduction

Patients with bipolar disorder (BD) experience a broad range of cognitive deficits in acute mood states of the illness with many persisting in remission (Bearden et al., 2001). The presence of cognitive impairments during remission suggests that these deficits may be related to the pathophysiology of the disorder. Targeted neurocognitive testing often demonstrate impaired response inhibition in patients with BD in a euthymic state (Robinson et al., 2006; Bora et al., 2009). Inhibition is an executive function that can be defined as the ability to suppress responses when they are inappropriate in a given context (Logan and Cowen 1984). The inability to inhibit responses relates to impulsive behavior, a clinically observable phenomenon in BD (Christodoulou et al., 2006). Extreme manifestations of impulsivity impair everyday functioning and represent important targets for treatment interventions (Evenden 1999; Moeller et al., 2001).

While poor inhibitory control has been reported in BD (Frangou et al., 2005; Torralva et al., 2011), studies have also demonstrated normal inhibitory control in euthymia (Townsend et al., 2012; Ibanez et al, 2012). These inconsistent results are likely due to methodological differences across studies. Complex tasks (for example a Stroop task) seem to implicate poor inhibition in euthymic BD (see Bora et al., 2009 for a review). These task designs may involve additional cognitive processes, for example increasing short term memory demands and shifting attention (Buchsbaum et al., 2005), which may cause difficulties in inhibition. On the other hand, more simple tasks like the Go/NoGo task are able to tap more directly into the inhibition processes by minimizing load on other cognitive processes. Studies using the Go/NoGo task have demonstrated normal inhibitory control in euthymic BD (Kaladjian et al., 2009; see Newman and Meyer 2014 for review). In other words, although a deficit in inhibition has been proposed in BD, using a very simple inhibition task seems to imply intact inhibition in euthymic BD.

However, despite behavioral performance, neuroimaging data have consistently demonstrated abnormal activations in BD relating to inhibition regardless of mood state (Hajek et al., 2013a). Decreased activations of the inferior frontal cortex (IFC) during inhibition tasks (Townsend et al., 2012; Blumberg et al., 2003) and structural alterations of the IFC are commonly found in BD (Stanfield et al.,2009; Hajek et al., 2013b), a region implicated for successful inhibition in healthy subjects (Horn et al., 2003). These findings are so robust that poor response inhibition mediated by changes in the IFC has been proposed to be an endophenotype in BD (Bora et al., 2009). In addition to decreased IFC activations in BD, data from a meta-analysis of neuroimaging studies related to inhibition (Hajek et al., 2013a) demonstrated that patients with BD in a euthymic state also had subcortical hypoactivations (i.e. basal ganglia) and cortical *hyperactivations* (specifically in the prefrontal cortex) together with normal performance. Hajek and colleagues (2013) therefore suggested that patients with BD in a euthymic state may compensate for subcortical hypoactivations or hypoactivations of the IFC by over activating adjacent prefrontal cortex, leading to normal performance. Unfortunately, the meta-analysis included studies with tasks of varying levels of complexity. As complex tasks recruit additional cognitive processes, many involving the prefrontal cortex, it is difficult to isolate brain regions specific to the inhibitory process. The use of complex tasks in the meta-analysis may possibly confound neurological findings. Therefore cortical activations involved in inhibitory processing in BD remain unclear and need to be further investigated.

On a neurophysiological level, an accurate reflection of inhibitory control is indexed by two distinct event related potential (ERP) components; the NoGo N2 and the NoGo P3 (De Jong et al., 1990; Jonkman et al., 2003; Smith et al., 2008; Kok et al., 2004). The NoGo N2 is associated with an early stage of the inhibition process, specifically the detection of conflict between an internal representation of a Go response and a NoGo response (Nieuwenhuis et al., 2003; Donkers and van Boxtel 2004). The NoGo P3 is a later component reflecting actual inhibition of the motor

system (Kok et al., 2004). Using source localization analysis with low resolution electromagnetic tomography (LORETA), both the NoGo N2 and the NoGo P3 have been shown to be most robust at fronto-central areas when responses have to be inhibited (Bokura et al., 2001; Fallgatter et al., 1997; Tekok-Kilic et al., 2001). Specifically the NoGo N2 has been shown to be generated in the anterior cingulate cortex (ACC) and IFC (Lavric et al., 2004; Pliszka et al., 2000; Bokura et al. 2001) and the NoGo P3 in the orbito-frontal cortex (Bokura et al., 2001). Given the inconclusive results regarding cortical activations relating to inhibition in BD, investigating inhibition using electrophysiology can be beneficial in isolating the specific cognitive subprocesses of inhibition.

Previous ERP studies in BD mainly focused on processes relating to allocation of attention to a stimulus. Many studies demonstrated lower P3 amplitudes (Bersani et al., 2015; Fridberg et al., 2009; Salisbury et al., 1999; Hall et al., 2009) in BD compared with healthy controls, yet not all studies corroborated these findings (Lahera et al., 2009; Souza et al., 1995). Importantly, most studies did not investigate inhibitory control in BD, but rather investigated stimulus processing in a standard oddball task where subjects had to respond to the rare stimuli instead of suppressing a response.

Two studies to date have investigated inhibitory control using a Go/NoGo task and ERP measures in BD (Michelini et al., 2016; Chun et al., 2013). Although both studies used a Go/NoGo task, results of these studies have been inconclusive regarding NoGo amplitudes relating to inhibition, with one study showing normal NoGo P3 amplitudes (Chun et al., 2013) and the other finding reduced NoGo P3 amplitudes together with reduced N2 amplitudes in BD (Michelini et al., 2016). Possible methodological limitations may have led to these differences. Firstly, the interpretation of ERP is largely complicated by confounding effects of mood state and as such, this may be an important factor in the interpretation of the inconclusive results regarding NoGo P3 in BD.

Elevated mood is known to influence cognition with evidence of cognitive deficits becoming more severe during manic and depressed episodes compared with euthymia (Martinez-Aran et al., 2004). In addition, state differences relating specifically to inhibitory control have been observed with decreased inhibitory control in mania (Larson et al., 2005) and hyperactive inhibition in depression (Langenecker et al., 2007). This is not surprising as impulsive behavior is a prominent symptom among individuals with mania and individuals with depression are more careful when responding in order to avoid errors. Therefore, state related inhibitory problems may have confounded the investigation. Elevated mood has been additionally found to influence ERP activity including P3 activations. Specifically, depressive state has been found to increase ERN, an ERP related to error detection and conflict monitoring (Morsel et al., 2014). Depressive state was also found to reduce P300 amplitudes relating to attention and memory (Kaya et al., 2007). Unfortunately, the study by Chun and colleagues (Chun et al., 2013) used patients with BD who were in a range of different mood states, which may have obscured their findings. While Michelini and colleagues, (Michelini et al., 2016) used a euthymic sample to investigate NoGo N2 and NoGo P3 in BD, the variation of the Go/NoGo task used was more similar to a cued continuous performance test that in fact does not load as highly on inhibition as a Go/NoGo task where a prepotent response has to be inhibited.

An additional methodological limitation of previous NoGo studies is that neither study (Michelini et al., 2016; Chun et al., 2013) accounted for effects of medications on ERP measures. While there is some evidence demonstrating that medications, specifically lithium and antipsychotics, do not influence ERP amplitudes (Strik et al., 1998; O'Donnell et al., 2004; Reeves and Struve et al., 2005), there are other studies that suggest that medications may influence ERP activity. Specifically, one study demonstrated that patients taking lithium have increased amplitudes compared with patients taking antipsychotics (Small et al., 1998). In addition, some studies have demonstrated changes in EEG in response to antipsychotics (Small et al.,

1989; Centorrino et al., 2014; De Bruijn et al., 2004). There is also evidence of benzodiazepines reducing ERP in patients with schizophrenia (de Bruijn et al., 2006) and healthy controls (Hayashi et al., 2000; Urata et al., 1996). It is therefore still unclear how medications impact EEG and may perhaps confound results.

In the present study, two subprocesses of response inhibition indexed by the NoGo N2 and NoGo P3 were investigated using a straightforward Go/NoGo task. Patients with BD in a euthymic state were compared with healthy controls in order to identify any dysfunction that may be related to the pathophysiology of the disorder. In line with previous research, patient with BD were expected to show normal performance on the inhibition task but differential neural activations relating to inhibitory processes. Specifically, reduced NoGo N2 amplitudes were expected (as in Michelini et al., 2016) and increased NoGo P3 amplitudes were expected in BD, just as cortical hyperactivations have been proposed in euthymia (Hajek et al., 2013a). In addition, the influences of different medications on the ERP activations were investigated.

Method

Participants

Twenty patients with BD and 18 healthy controls participated in the study. Patients were recruited from the St. Norbertus psychiatric hospital (Duffel, Belgium) and from the Psychiatric Centre Brothers Alexians (Boechout, Belgium) and had participated in a previous research study (Morsel et al., 2014).

Diagnosis of the patients according to DSM-IV-TR criteria was confirmed using a semi-structured interview. All of the patients were in a euthymic state at the time of testing. This was assessed using the Beck Depression Inventory (BDI-II) (Beck et al., 1961) and the Hamilton depression rating scale (HDRS) (Hamilton 1960) to confirm the absence of depressive symptoms (less than 8 on the HDRS) and the

Young Mania Rating Scale (YMRS) (Young et al., 1978) to confirm the absence of manic symptoms (less than 7 on the YMRS). Patients were excluded from the study if they had a neurological disorder, history of brain injury, drug or alcohol dependence in the last year or intellectual disability. Patients with BD were taking a range of medications, specifically mood stabilizers (85%), antidepressants (35%), atypical antipsychotics (70%) and benzodiazepines (20%).

All subjects had normal or corrected-to-normal vision. Control participants were similar to the study group in terms of gender, age, education level and dominant hand. Controls were excluded from the study if they had a history of a psychiatric disorder.

Ethical approval for this study was obtained by the medical ethics committees of both hospitals and carried out in accordance with the latest version of the Helsinki Declaration. All participants gave their written informed consent.

Material

Go/No-Go task

All participants performed the Go/No-Go task (Donders 1969). The task consisted of Xs (Go stimuli) presented on 70% of trials and Os (No-Go stimuli), presented on 30%of trials. Each letter was presented for 100 ms at the center of the screen. Stimulus size of the Xs and Os was approximately 18 mm x 12 mm. The stimuli were presented pseudo-randomly; each No-Go stimulus was followed by at least three Go stimuli before the presentation of the next No-Go trial. The interstimulus intervals were randomized at 2000, 2250, 2500, 2750 or 3000 msec.

Participants were instructed to respond to the letter X and not to respond when the letter O was presented. A response comprised of pressing a button on a button-box with the index finger of the dominant hand as quickly as possible following stimulus presentation. There were 3 blocks of 150 trials and in between each block, participants could take a break. Equal emphasis was placed on speed and

accuracy. Subjects did not receive any feedback regarding their performance. The task lasted 20 minutes.

Electrophysiological measurements

The electroencephalogram (EEG) was sampled at 5000 Hz and electrophysiological signals were recorded using 32 active electrodes fixed on an actiCAP, with a DC amplifier (Brain Products GmbH (Germany)) at the Fz, FCz, Cz, Pz, Oz, F7/8, F3/4, FC5/6, FC1/2, T7/8, C3/4, CP5/6, CP1/2, P7/8, P3/4 and O1/2 sites, according to the extended international 10-20 system. In addition, horizontal electro-oculogram (EOG) was recorded from the outer canthus of each eye and vertical EOG was recorded from infra- and supraorbital electrodes placed in line with the pupil of the right eye. Electrode impedances were kept below 10kΩ.

Behavioral data analyses

Reaction times, percentage of correct hits for Go stimuli and errors of commission (incorrectly responding to NoGo stimuli) were subjected to separate independent samples t-tests to compare patients with BD and controls.

For the analysis of clinical variables (age, education, hand, gender and mood state), ANOVA (in cases of continuous variables) or Chi-square tests were performed to compare frequencies between groups.

ERP analyses

ERP data were collected using Brain Vision Analyzer 2.1. All electrodes were referred to an electrode which was situated between Cz and Pz and grounded at AFz and were later re-referenced offline to the average of T7 and T8. A band-pass filter

between .02 Hz and 15 Hz was applied to the raw data and the EEG was downsampled to 250 Hz.

The EEG was corrected for EOG artifacts using the Gratton and Coles algorithm (Gratton et al., 1983). ERPs were time-locked to stimulus onset and averaged for correct responses relative to a 200 msec pre-stimulus baseline. N2 amplitudes were determined for correct Go trials and correctly inhibited NoGo trials by calculating the most negative peak in the 200-350 msec time window after stimulus onset. P3 amplitudes were determined for correct Go trials and correctly inhibited NoGo trials by calculating the most positive Go and NoGo peaks in the 250-550 msec time window after stimulus onset. Fronto-central electrodes (FCz and Cz) were investigated where maximal NoGo N2 and P3 amplitudes were expected (Bokura et al., 2001; Fallgatter et al., 1997; Tekok-Kilic et al., 2001).

Statistical analyses were performed using SPSS 20.0. In order to ascertain whether the NoGo task used in this study elicited increased fronto-central NoGo N2 and NoGo P3 amplitudes compared with Go amplitudes, repeated measures GLM were first conducted using Group (bipolar vs. control) as the between-subjects factor and Electrode (FCz and Cz) and Trial type (Go vs. NoGo) as the within-subjects factors. N2 and P3 were separately investigated.

Analysis of medication effect

Effects of medications on NoGo N2 and NoGo P3 amplitudes were examined in the patient group. Each medication (mood stabilizers, antidepressants, antipsychotics and benzodiazepines) was coded ‘on’ or ‘off’ for each BD patient. As inhibition was the focus of this study, only the NoGo trials were analyzed. The medication analysis was conducted in the same way as the electrophysiological data analysis using repeated measures GLM with each medication separately assessed as the between-subjects factor and Electrode as the within-subjects factor.

Results

Clinical and Demographic data

Clinical and pharmacological treatments of the participants are presented in Table 1. The two groups did not significantly differ in age, gender, education level or dominant hand. There was a significant effect of residual depressive symptoms with higher scores on the HDRS and BDI-II scales in the BD group. Residual manic symptoms did not differ amongst the groups.

Table 1: Overview of demographic and clinical characteristics

	Bipolar disorder (n=20)	Control (n=18)	*test statistic*	*p-value*
Gender	50% Male	40% Male	X^2=.117	.757
Age, mean years (SD)	44 (12.05)	42 (15.09)	t(36)=.463	.632
Education level (mean rank)	2.0 (.72)	2.22 (.55)	X^2=2.751	.252
Hand	75% Right	94% Right	X^2=2.694	.184
Clinical rating scale, mean, (SD)				
YMRS	2.316 (2.06)	1.222 (1.93)	t(36)=1.667	.104
HDRS	3.00 (2.62)	.722 (1.18)	t(36)=3.372	.002*
BDI-II	10.474 (9.08)	3.667 (2.89)	t(36)=3.036	.005*
Medication				
Mood stabilizers	17 (85%)			
Antidepressants	7 (35%)			
Atypical antipsychotics	14 (70%)			
Benzodiazepines	4 (20%)			
Age of onset, mean (SD)	31.84 (13.75)			
Number episodes	10.21 (9.77)			
Suicide attempts	1 (1.37)			

*p<.01, YMRS=Young Mania Rating Scale (30; Young, 1978), HDRS=Hamilton Depression Rating Scale (29; Hamilton, 1960), BDI-II= Beck Depression Inventory (31; Beck, 1966). Education level subdivided in a low (1), medium (2) and high (3) level in accordance with the Belgium education system.

Go/ No-Go task

Behavioral data

Mean reaction times to Go stimuli, percentage of correct hits for Go trials and percentage of commission errors are presented in Table 2. There were no group differences in any of the conditions (RT: t(36)=.159, p=.875; error: t(36)=1.31, p=.198; correct hit: t(36)=1.08, p=.288). As expected, subjects had no difficulty correctly classifying and responding appropriately to stimuli.

Table 2: Mean (SD), reaction times (RT) to standard stimuli, percent correct hits and percent errors of commission

	Bipolar disorder	Control
RT (ms) to standard	387.95 (55.51)	385.20 (50.43)
% correct hits	97.94% (2.32)	97.81% (3.49)
% errors of commission	9.81% (9.92)	6.26% (6.17)

Electrophysiological data

Figure 1 illustrates the grand averaged waveforms at the fronto-central electrodes (FCz and Cz) for Go and NoGo trials. Analysis of NoGo N2 revealed a significant main effect of Trial (F[1,36]=19.674, p<.001; d'=.41), indicating more negative N2 amplitudes for NoGo trials (mean= -.968μV, SD=2.78) than for Go trials (mean= -.081μV, SD=2.35). Similarly, NoGo P3 analyses revealed a significant main effect of Trial (F[1,36]=4.781, p=.035, d'=.031) with larger P3 amplitudes for NoGo

trials (mean=5.349µV, SD=3.64) than for Go trials (mean=4.331µV, SD=2.84), indicating that the task manipulation was successful.

There was no significant main effect of Electrode for N2 (F[1,36]=3.747, p=.061) or P3 (F<1), nor was there a significant interaction between Electrode and Group for N2 (F[1,36]=3.763, p=.060) or P3 (F<1). There were no significant interactions between Trial and Group, Trial and Electrode or between Trial, Electrode and Group for N2 or P3 (all Fs<1), nor was there a significant main effect of Group for either ERP measure (N2: F[1, 36]=2.540, p=.120; P3: F[1,36]=3.024, p=.091).

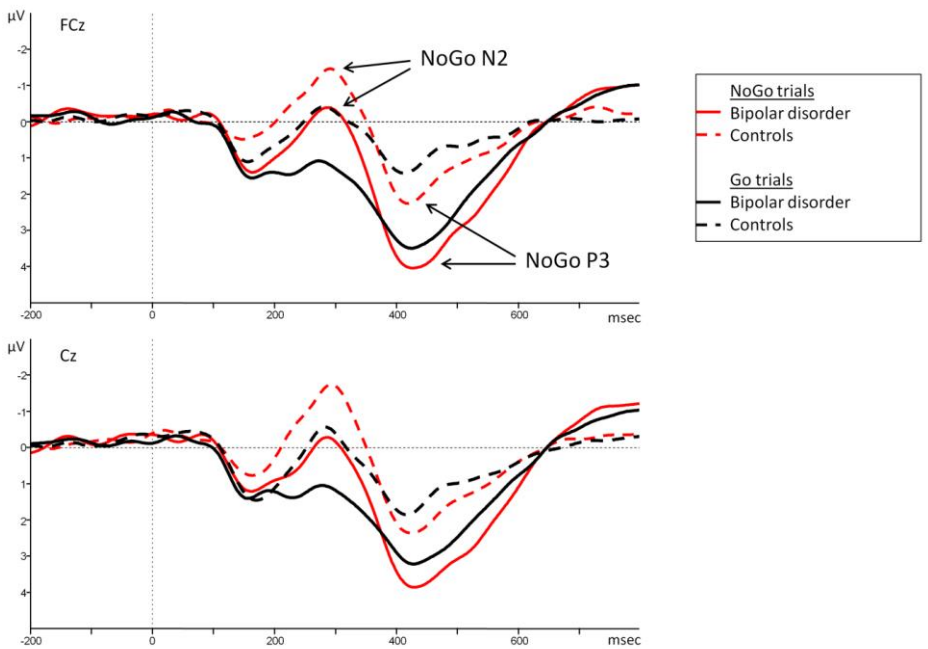

Figure 1: Grand average stimulus-locked waveforms for Go and NoGo trials in patients with bipolar disorder and healthy controls. Frontocentral electrodes FCz and Cz are depicted. Stimulus onset is at 0 msec.

Controlling for medications

Figure 2 illustrates the effects each medication had on the NoGo N2 and NoGo P3 amplitudes in patients with BD. There were no main effects of medication on NoGo N2 amplitudes (benzodiazepines: $F[1,17]=1.929$, $p=.183$; mood stabilizers ($F[1,17]=2.113$, $p=.163$); antidepressants or antipsychotics ($Fs<1$)). There were no main effects of Electrode (all $Fs<1$), nor were there significant interactions between benzodiazepines and Electrode ($F<1$), mood stabilizers and Electrode site ($F[1,17]=3.287$, $p=.087$), antidepressant and Electrode or antipsychotics and Electrode ($Fs<1$).

However, effects of medication on NoGo P3 revealed a significant main effect of benzodiazepines on NoGo P3 amplitudes ($F[1,17]=5.183$, $p=.036$, $d'=1.45$). Patients taking benzodiazepines had smaller NoGo P3 amplitudes (Mean=2.99μV, SD=1.98) compared with patients who were not taking benzodiazepines (Mean=7.06μV, SD=3.45). There was no main effect of Electrode, nor was there a significant interaction between benzodiazepines and Electrode sites (both $Fs<1$). No significant main effects of mood stabilizers ($F[1,17]=2.182$, $p=.157$), antidepressants ($F[1,17]=1.548$, $p=.230$) or antipsychotics ($F<1$) were found to influence NoGo P3 activations. There were also no significant interactions between mood stabilizers and Electrode site, antidepressant and Electrode or antipsychotics and Electrode (all $Fs<1$).

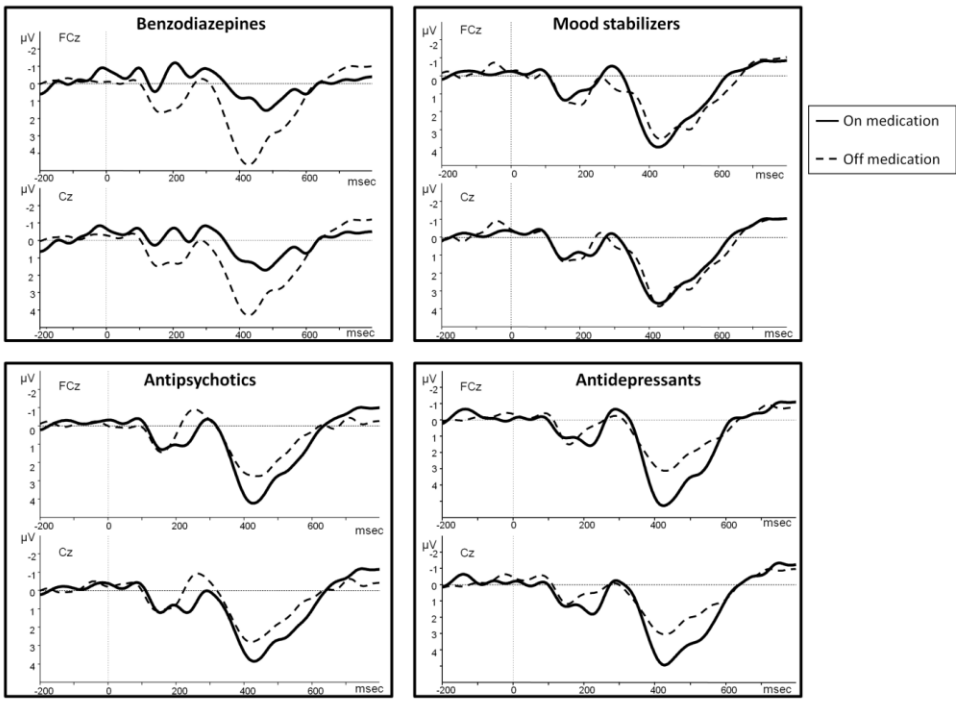

Figure 2: Grand average stimulus-locked waveforms of NoGo trials for patients with bipolar disorder on and off medications (benzodiazepines, mood stabilizers, antipsychotics and antidepressants). Frontocentral electrodes FCz and Cz are depicted. Stimulus onset is at 0 msec.

Follow up analyses were conducted based on the significant effects of benzodiazepines on the ERP. As only 4 patients were taking benzodiazepines, behavioral and ERP analyses were re-run without these patients in order to assess for any Group differences. No differences were found amongst the behavioral results; there were still no Group differences in any of the conditions (RT: $t(32)=.198$, $p=.844$; errors of commission: $t(32)=1.41$, $p=.168$; correct Go hit: $t(32)=1.04$, $p=.305$).

Figure 3 illustrates the ERP waveforms for Go and NoGo trials among the subset of patients with BD who were not taking benzodiazepines and healthy controls. Excluding patients taking benzodiazepines revealed a trend of enhanced

NoGo N2 amplitudes among patients with BD (Mean=.142µV, SD=2.66) compared with controls (-1.672µV, SD=2.67), although this trend was not statistically significant (F[1, 32]=4.042, p=.053, d'=0.68). There was no significant main effect of Electrode nor was the interaction between Electrode and Group significant (both Fs<1). There was a significant Group difference for NoGo P3 amplitudes (F[1,32]=4.292, p=.046, d'=0.71), which was not present in the initial analysis indicating that patients with BD have increased NoGo P3 amplitudes (Mean= 6.969µV, SD=3.22) compared with controls (Mean=4.523µV, 3.65). As before, there was no main effect of Electrode (F[1,32]=1.278, p=.267), nor was the interaction between Electrode and Group significant (F[1,32]=1.519, p=.227).

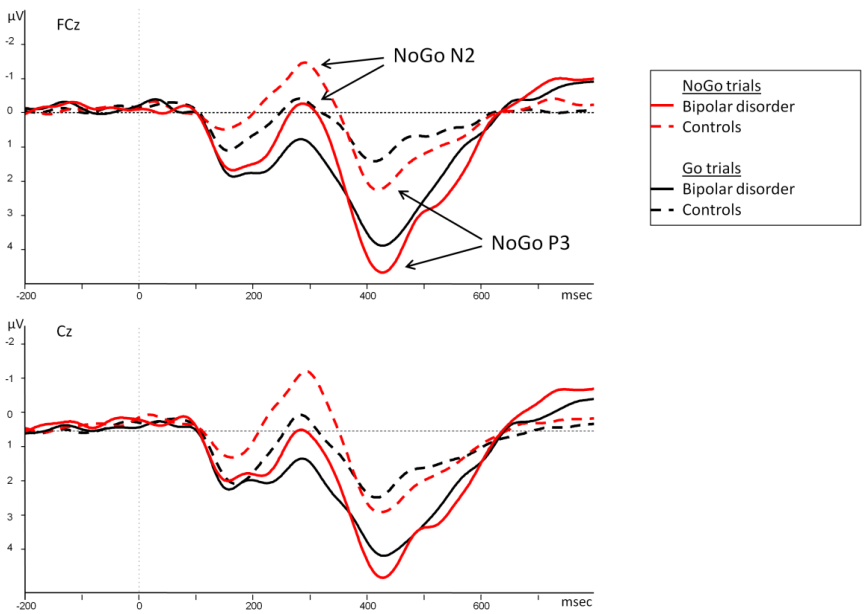

Figure 3: Grand average stimulus-locked waveforms of Go and NoGo trials among the subset of patients with bipolar disorder who are off benzodiazepines and healthy controls. Frontocentral electrodes FCz and Cz are depicted. Stimulus onset is at 0 msec.

Correlations with residual mood state

Residual depressive symptoms (measured by the HDRS, BDI-II) were found to be present in the BD group (see Table 1). Therefore, post-hoc correlation analyses between the BDI-II rating scale and NoGo N2 and NoGo P3 amplitudes were calculated in order to see whether there was a relationship between residual mood and electrophysiological measures. The BDI-II scale is a subjective measure which is able to tap into depressive symptoms in healthy subjects and in individuals with BD. Correlations were performed separately for each group and patients taking benzodiazepines were excluded. As there was no interaction between the ERP amplitudes and Electrode, correlation analyses were conducted on the mean NoGo N2 and NoGo P3 of electrode FCz and Cz.

None of the correlations were statistically significant. However, looking at the correlation coefficients, there was a negative relationship with a medium effect size between the BDI-II scores and the NoGo N2 amplitudes (r=-.246, p=.378) and a positive relationship with a medium effect size between the BDI-II scores and NoGo P3 amplitudes (r=.205, p=.463), indicating that as depressive symptoms increase, the NoGo N2 amplitudes decrease and the NoGo P3 amplitudes increase. These relationships were not present in the control group (NoGo N2: r=-.028, p=.001; NoGo P3: r=-.038, p=.234). An additional relationship with a medium effect size was present between the NoGo N2 and NoGo P3 amplitudes in the BD group (r=.392, p=.133) and not in the control group (r=.171, p=.511).

Discussion

The current study investigated two subprocesses of response inhibition in patients with BD using a Go/NoGo task in conjunction with the NoGo N2, an early ERP measure of conflict detection and the NoGo P3, an ERP measure of inhibitory processing. Patients with BD in a euthymic state were compared with matched

controls. This study additionally assessed the effects of medications on ERP activations. Results showed normal behavior on the inhibition task together with marginally reduced NoGo N2 amplitudes and *increased* NoGo P3 amplitudes in patients with BD, as expected, indicating overactivation of cortical fronto-central areas during NoGo trials. Importantly, these results were only obtained when taking the effects of medications (specifically benzodiazepines) into account.

Behavioral results of the current study are in line with previous reports of normal inhibition in euthymic BD during a simple task (Townsend et al., 2012; Ibanez et al., 2012; Kaladjian et al., 2009; Newman and Meyer 2014**)**. Although studies using more complex inhibition tasks have demonstrated aberrant inhibition in BD (Bora et al., 2009), more complex tasks may require the engagement of additional executive properties, as opposed to a simple task which may tap more directly into the inhibition process. It is thus clearly beneficial to use a simple task when investigating inhibition and the underlying neural processes in BD. Importantly, studies have shown that using easy tasks can show altered brain activity uncompromised by differences in task performance (see Kronhous et al., 2006; Van Hecke 2010), thereby allowing clear identifications of neural abnormalities.

Results of the current study showed discrepancies between normal behavior and altered neural responses during the inhibition task in BD, enabling more insight into inhibitory processing in BD. While there is robust evidence demonstrating structural alterations of the IFC in BD and reduced IFC activations during inhibition tasks (ie, Townsend et al., 2012; Blumberg et al., 2003; Stanfield et al., 2009; Hajek et al., 2013b), additional cortical activations using fMRI (Hajek et al., 2013a) and NoGo P3 (Michelini et al., 2016; Chun et al., 2013) have remained unclear due to methodological limitations. The current study was able to tap directly into cortical activity relating to different subprocesses of inhibition in euthymic BD. The finding in the current study of reduced NoGo N2 amplitudes in BD, an index of an early stage of conflict detection, taken together with previously reported evidence that NoGo N2 is generated by the IFC (Lavric et al., 2004; Pliszka et al., 2000), supports these well

documented neuroimaging findings relating to abnormal activations of the IFC in BD. In addition, reduced NoGo N2 amplitudes support previous reports of impaired conflict monitoring in BD (Michelini et al., 2016; Morsel et al., 2014; Ethridge et al., 2012). The additional finding of *increased* fronto-central NoGo P3 amplitudes found in the current study, together with evidence that NoGo P3 is generated in the prefrontal cortex (Eimer et al., 1993; Kopp et al., 1996; Bokura et al., 2001) provided evidence that patients with BD compensate for abnormalities in early stages of the inhibitory process by overactivation of additional cortical areas (such as the prefrontal cortex), leading to normal performance (as suggested by Hajek et al., 2013a).

This compensatory system relating to inhibition can be explained further. Reduced NoGo P3 activations would suggest difficulties in inhibitory control, which often coincides with more behavioral errors of commission. However, results of the current study show that patients with BD could inhibit successfully in an easy task, and this coincided with increased NoGo P3 activations, suggesting that patients with BD had to invest more effort in order to perform as well as controls, corroborating the finding of Hajek and colleagues (Hajek et al., 2013a). Results of the study extend current knowledge regarding information processing capacities in BD, suggesting that equal performance on a simple task requires more effort in BD, reflected by increased cortical activity.

Reduced NoGo N2 and increased NoGo P3 amplitudes found in BD in the current study were only present when patients taking benzodiazepines were excluded from the study, suggesting that benzodiazepines reduce NoGo P3 amplitudes significantly. These findings are in support of previous findings in schizophrenia implicating that benzodiazepines reduce ERPs (i.e.,De Bruijn et al;, 2004; Hayashi 2000; Urata et al., 1996) as well as findings that other medications (lithium, antipsychotics) do not affect ERP amplitudes in BD (Strik et al., 1998; O'Donnell et al., 2004; Reeves and Struve 2005). Results of the current study are critical as most ERP studies do not take the effects of specific medications into

account in the P3 analyses, and it is possible that decreased NoGo P3 amplitudes found in a previous NoGo study in BD (Michelini et al., 2016) are simply the result of medications and not actual underlying deficits in BD. However, as only 4 patients in the current study were taking benzodiazepines, it is possible that the effects of this drug treatment on NoGo P3 amplitudes was a false-positive result or an over-estimation of the magnitude of the association. In addition, benzodiazepines are often taken as needed rather than on a daily basis, and patients taking a higher dosage (or more frequent usage) may have more adverse side effects, including depression, potentially interfering differently with cognitive abilities and ERP activations. While excluding patients using benzodiazepines from electrophysiological research may be beneficial, this may result in leaving out a population of patients with different symptoms than BD patients who are not taking benzodiazepines. Larger confirmatory studies are needed to explore the effects of benzodiazepines in the same patients, on and off the drug.

Most studies investigating ERP in BD categorize patients as a group without taking effects of symptom severity on ERP activity into account. However, in the present study, correlation analyses were additionally performed between residual depressive symptoms and ERP measures. Depressive symptoms assessed by a subjective measure were related to lower NoGo N2 amplitudes and greater NoGo P3 amplitudes with a medium effect size in the BD group and not in the control group. This increase in NoGo P3 could be related to a hypersensitivity to incorrectly responding which is found in patients with depression (Cavanagh et al., 2011) and anxiety traits (Sehlmeyer et al., 2010) and is in line with previous reports of residual depression influencing P3 activations (Maekawa et al., 2012; Kaya et al., 2007. These correlations may alternatively suggest an underlying group effect rather than a true relationship. However, the correlations need to be interpreted with caution as none were statistically significant. In addition, while results of the correlations may suggest that the NoGo P3 is state dependent rather than a compensatory mechanism in BD patients, an additional relationship found in the current study between NoGo N2 and

NoGo P3 amplitudes only in the BD group supports the suggestion of the current study that the P3 is a compensation mechanism in BD.

Patients in the current study did not have more residual manic symptoms compared with healthy controls and an investigation of residual manic symptoms on NoGo P3 could not be performed. As impulsivity is a prominent clinical feature of mania with evidence of decreased inhibitory control in mania (Larson et al., 2005), residual manic symptoms may also influence the ERP relating to inhibition. For this reason, future studies should include an investigation of residual symptoms as these may have additional state related influences on inhibitory processing in BD.

Although poor inhibition is a prominent clinical feature of BD, including impulsivity and risk behavior (i.e., suicide attempts and substance abuse) (Christodoulou et al., 2006), results of the current study suggest that the underlying neural deficits cannot simply be written off as an impaired inhibitory system as proposed (Bora et al., 2009). It is possible that observed behavioral abnormalities of inhibition may be related to additional cognitive deficits present in BD, such as abnormal information processing, conflict monitoring, abnormal emotional responses to the processing of information or a combination of these. While results of the current study extend current knowledge regarding inhibitory processing in BD, further research relating to the neural underpinnings of poor inhibition is critical for the advancement of treatment targets in BD. Next to pharmaceutical interventions, cognitive remediation therapy is also emerging as an important treatment strategy in BD (see Bowie et al., 2013 for a review). Our results may suggest that in order to improve inhibitory processes, cognitive remediation needs to address other abovementioned cognitive deficits as well. However, further research is needed.

An important limitation of the current study is the small sample size. Studies including more participants are necessary in order to make more concrete conclusions. An additional limitation of the study is that the suggested compensatory inhibitory mechanism may not extend to all cases. There is evidence of increased impulsive behavior (more errors of commission) in patients with more complicated

bipolar disorder, for example with many past mood episodes, substance use disorder or suicide attempts (Swann et al., 2005). It is important to note that even a simple task could include some elements of other cognitive processes, such as attention. While behavioral data of the current study suggested that the participants appeared to have no problems attending to the current task, it would be interesting for future studies to directly manipulate attention during a Go/NoGo task, by varying attentional load, allowing further investigations into the inhibitory process uncomplicated by attention. A final limitation is that the outcome of the current study may seem to suggest that no intervention is necessary in order to improve response inhibition in patients with BD, as compensatory processes effectively deal with impairment in inhibition. However, results of the current study cannot be easily generalized to other or more difficult tasks. It is likely that complex tasks require more compensatory effort, and available resources may not always suffice. Compensatory processes may break down leading to behavioral impairments, as is commonly seen in more complex inhibition tasks (Bora et al., 2009). Therefore, despite evidence for normal inhibitory performance in BD, nevertheless patients with BD might still benefit from interventions targeting inhibitory control to accommodate for more complex real life situations.

Conclusion

Patients with BD in a euthymic state demonstrate marginally reduced NoGo N2 and increased NoGo P3 amplitudes at fronto-central electrodes during a simple inhibition task compared with healthy controls when patients using benzodiazepines were excluded from the study. In addition, normal task performance was found. These findings suggest that patients with BD have to invest more effort in order to perform as well as healthy controls and they appear to compensate by over-activating cortical (fronto-central) areas related to inhibitory processing.

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Chapter 5

Electrophysiological (EEG) evidence for reduced performance monitoring in euthymic bipolar disorder

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Abstract

Objectives Apart from mood episodes, many cognitive deficits are present in bipolar disorder (BD). Performance monitoring is an important aspect of executive functioning and involves continuous monitoring of behaviour and making subsequent changes when an error is made. On a neurophysiological level, the error-related negativity (ERN), an event related brain potential (ERP) generated in anterior cingulate cortex (ACC), reflects this process of performance monitoring. Abnormal ERN amplitudes have been observed in many major psychiatric disorders. However, despite conflicting evidence regarding the role of the ACC in BD, no studies to date have investigated performance monitoring as reflected in the ERN in BD.

Methods Sixteen patients with BD in a euthymic state and fourteen matched healthy controls performed a speeded two-choice reaction-time paradigm (Flankers task) while EEG measures were obtained. Behavioral and ERP measurements were analyzed for the two groups.

Results The BD patients, although euthymic, scored higher on depressive symptoms than healthy controls. While no behavioural group differences were found, BD patients displayed lower ERN amplitudes than healthy controls when controlling for effects of residual mood.

Conclusions The lower ERN amplitudes in the BD group reflect reduced performance monitoring and extend current knowledge of executive functioning in BD. Importantly, these findings go a long way to resolve the contradictory results regarding ACC involvement in BD by showing that taking into account residual mood may greatly influence error-related ACC activations and is critically important in understanding cognitive deficits in BD.

Introduction

A wide range of cognitive disturbances persist in bipolar disorder (BD) even in the absence of acute mood episodes (Bearden et al., 2001; Bora et al., 2009). These cognitive deficits may be additionally affected by the mood state, becoming more severe during mood episodes (Martinez-Aran et al., 2004). However, the presence of cognitive dysfunction in remission indicates that cognitive impairments are core symptoms of the illness and may be connected to the BD pathophysiology. Behavioral deficits in executive functions are one of the most consistently demonstrated cognitive deficits in BD (Bora et al., 2009; Martinez-Aran et al., 2004; Martinez-Aran et al., 2002). Performance monitoring is a central function of executive control and refers to the process of continuously keeping track of one's behavior and goals and making subsequent behavioral changes when errors occur (Ullsperger 2006). Although successful performance monitoring has important implications for daily life functioning (Ullsperger 2006), to date, no one has investigated performance monitoring in BD.

The anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) are known to play a central role in performance monitoring and conflict resolution (van Veen and Carter 2006), with the ACC as the presumed neural substrate of error detection (see e.g. De Bruijn et al., 2009). However, neuroimaging data of BD patients in remission (euthymic) have yielded inconsistencies regarding the pattern of their dysfunction. On the one hand, using the Stroop task (Stroop 1935), a cognitive interference task used to investigate executive control, reduced activation of ACC and functional over-activation of DLPFC has been observed (Gruber et al., 2004). On the other hand, other studies showed *normal* ACC-DLPFC activation in BD patients while performing the Stroop task, and rather observed abnormal rostroventral prefrontal cortex (rvPFC) activation (Blumberg et al., 2003; Strakowski et al., 2005; Kronhaus et al., 2006), an area that has repeatedly been related to inhibition (Jonides et al., 1998; Levesque et al., 2003). In short, studies that investigated executive control processes in

euthymic BD patients have yielded inconsistent results, especially with regard to ACC involvement (see review Melcher et al., 2008).

Using electrophysiology, a sharp negative event-related brain potential (ERP) has been identified peaking 50-100 ms after an erroneous response. This ERP component is also known as the error negativity (Ne) or the error-related negativity (ERN) (Falkenstein et al., 1990; Gehring et al., 1993; Falkenstein et al., 2000) and is thought to reflect error-detection and performance-monitoring processes. Localization studies and later fMRI studies have demonstrated that the ERN is generated in the ACC (Dehaene et al., 1994; Ullsperger and von Cramon 2001; Ridderinkhof et al., 2004) and can thus be considered as an indirect measure of error-related ACC activation (see e.g., Debener et al., 2005). Despite the controversy over the role of the ACC in BD and the known problems in executive functions, no studies to date have used ERN to investigate performance monitoring in BD.

Performance monitoring has been extensively investigated in other major psychiatric disorders (for an overview see De Bruijn and Ullsperger 2011). Patients with schizophrenia are known to display decreased ERN amplitudes compared with controls (Alain et al., 2002; Bates et al., 2002; Bates et al., 2004; Houthoofd et al., 2013; Kim et al., 2006), indicating abnormal activation in response to making an error. It has been proposed by Olvet and Hajcak (2008) that this is a result of a general failure of internal monitoring of errors present in psychotic disorders. Decreased ERN amplitudes have been found in patients presenting with a psychotic disorder regardless of diagnosis (Minzenberg et al., 2014; Foti et al., 2012). In other words, lower ERN amplitudes may be related to the pathophysiology of psychotic disorders. Olvet and Hajcak (2008) further proposed that differences in the ERN patterns may be directly related to the nature of the disorders. For example, patients with mild depression, exhibiting an increased sensitivity to mistakes (Elliott 1998) have shown *increased* ERN amplitudes compared with controls (Holmes and Pizzagalli 2008; Chiu and Deldin 2007; Ruchsow et al., 2006a), while subjects with disorders characterized by insensitivity to errors, such as substance abuse (Fanken et

al., 2007; Easdon et al., 2005) or borderline personality disorder (Ruchsow et al., 2006b; De Bruijn et al., 2006a) have shown lower ERN amplitudes compared with controls. Therefore, distinct ERN patterns may characterize different disorders. Abnormal ERN amplitudes may also be the result of different states of a disorder. While patients with moderate depression show increased ERN amplitudes, patients with severe depression do not show this increase (Schrijvers et al., 2008) suggesting that the severity of the depression influences performance monitoring.

However, given the clinical and cognitive similarities between BD and other psychiatric disorders and increasing evidence of decreased ERN amplitudes in psychotic disorders as opposed to increased ERN amplitudes in depression, it is essential to investigate performance monitoring in bipolar disorder.

In the present study, we investigated performance monitoring and the related ERN amplitudes in BD using a speeded two-choice reaction-time paradigm. Using patients in a euthymic state removes the potential influence of mood state, allowing an identification of state-independent (trait) abnormalities that may be more related to the pathophysiology of the disorder and therefore may indicate pathogenic risk factors rather than effects of symptomatic states. However, the presence of low level residual depression symptoms are common in euthymic BD patients (for example, see Martinez-Aran et al., 2004) and may impact cognitive performance (Clark and Iversen 2002; Ferrier et al., 1999) especially in the field of performance monitoring (Schrijvers et al., 2008). Therefore, it is necessary to control for influences of residual depression symptoms on the amplitude of the ERN. A subjective (self-report) measure of depression (Beck Depression Inventory; BDI-II) (Beck et al., 1961) was used to assess residual depression symptoms. Given the similarities between BD and psychiatric disorders that are known to be characterized with reduced ERNs (e.g. schizophrenia) and the repeatedly demonstrated impairments in executive functioning, we expected decreased performance monitoring in BD.

In order to investigate the specificity of abnormal performance monitoring in BD indexed by the ERN, we also assessed the stimulus-locked ERP components N1, N2 and P3 to control for possible between-group differences in perceptual and/or attentional processes.

Materials and Methods

Subjects

Twenty patients (11 male; mean age 46.85 years, SD=10.8) and 19 healthy controls (8 males; mean age 41.71, SD= 14.6) were recruited for the study. Patients with a DSM-IV-TR diagnosis of bipolar disorder, as assessed by a semi-structured interview were included. Clinical evaluation of the patient group was done by means of the Hamilton depression rating scale (HDRS) (Hamilton 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). A maximum score of 8 on the HDRS indicating the absence of depression and a maximum score of 6 on the YMRS indicating the absence of mania was necessary for inclusion in order to obtain a sample of euthymic bipolar disorder patients.

The patients were recruited from the Psychiatric hospital St. Norbertus hospital, Duffel, Belgium as well as Psychiatric Centre Broeders Alexianen, Boechout, Belgium and were currently in-patients at the hospital. Patients with other disorders that could be related to neuropsychological impairment (significant physical or neurological illness, a history of head injury, substance abuse or dependence in the last year, mental retardation) were excluded.

The patients were treated with a range of different medications. All patients were taking mood stabilizers, and some were treated with additional atypical antipsychotics (n=10), antidepressants (n=8), and benzodiazepines (n=4).

The control group consisted of healthy volunteers who were matched to the patient group according to age (t=0.773, p=0.12), gender (Fisher's exact test, x^2=

1.16, p=0.24) and education level, subdivided in a low, average and high level in accordance with the Belgian educational system (x^2=2.16, p=0.34). Control participants completed the same clinical rating scales as the patients.

The patients were tested in the recruiting hospital (16 patients in the Psychiatric hospital St. Norbertus, Duffel and 4 patients in the Psychiatric Centre Broeders Alexianen, Boechout) and the controls were tested either in the psychiatric hospital in Duffel (10 subjects) or at the University of Antwerp in similar laboratory conditions (9 subjects).

All participants gave their written informed consent after the nature of the study had been fully explained to them. The study was carried out in accordance with the latest version of the Helsinki Declaration and was approved by the medical ethics committee of the participating hospitals.

Material

Residual mood assessment

All participants were assessed for residual depression symptoms using the Beck Depression Inventory (BDI-II) (Beck et al., 1961; van der Does 2002). The BDI-II is a self-rating scale that assesses the presence of depression symptoms and is able to capture depressive symptoms in both patients and controls.

Flankers task

All participants performed a modified Eriksen flankers task (Eriksen and Eriksen 1974). Subjects had to respond to a central letter (H or S) of a letter string while ignoring compatible flankers (HHHHH, SSSSS) or incompatible flanking stimuli (HHSHH, SSHSS). Equal emphasis was placed on speed and accuracy.

Previous ERP studies have demonstrated that accuracy can affect ERN amplitudes (Gehring et al., 1993), therefore, in order to ensure that error production was similar in the two groups individual RT deadlines were calculated at the start of the experiment (see De Bruijn et al., 2006a). Personal maximum RT was the time that a subject needed to respond in order to avoid feedback indicating that the response was too late. To set their RTs, all subjects first performed a 60- trial practice block following verbal instructions, with the initial RT deadline being set at a relatively long limit of 800 msec. After completion of the practice session, the participants' average RT and standard deviations of the correct responses were computed. Subsequently, the RT deadline for each individual participant was determined by adding 0.5 SD to this mean RT (cf. De Bruijn et al., 2006a; De Bruijn et al., 2004).

The experimental phase consisted of 10 blocks of 50 trials each, with a self paced break between every block. Verbal encouragement was given to keep performance accuracy at around 80-90%. In addition, in order to keep up the performance accuracy level, the RT deadline was adjusted throughout the task by adding or subtracting 0.5 SD to the mean RT depending on whether error rates were above or below 10%.

Visual feedback consisted of a yellow, blue or red rectangle indicating a correct response, error or too late response respectively. Responses were considered too late when RTs exceeded the assigned deadline.

Electrophysiological measurements

The electroencephalogram (EEG) measurements were made with a full set of EEG Brain Products GmbH (Germany). This set contains 32 active electrodes that are placed on an actiCAP, a power supply, and a DC amplifier that takes the EEG signal coming from the electrodes and enhances revenue from an analogue to a digital signal (sampling frequency of up to 5000 Hz). This digital signal is then passed

through the USB adapter to a computer with the software Brain Vision Recorder 1.10 recording software.

Electrodes were placed at the midline (Fz, FCz, Cz and Pz) as well as lateral locations (OZ,F7/8,F3/4,FC5/6,FC/2,T7/8,C3/4,CP5/6,CP1/2,P7/8,P3/4,01/2) in accordance with the extended international 10-20 systems. In addition, electrodes were placed above, below, left and right of the eyes. Electrode impedances were kept below 10Ω.

Procedure

Subjects were screened using the clinical rating scales. Participants then filled out the self-report BDI-II questionnaire. All clinical rating scales were assessed by one experienced clinician (A.T) and the experimental testing (the flankers task in conjunction with the EEG testing) was followed by a second clinician. Participants performed a practice block of 60 trials in order to assess that each participant clearly understood the task. Responses were considered late when the individual RT's exceeded the assigned deadline. The experimental phase lasted 35 minutes including breaks.

Behavioral data analyses

Individual average reaction times and percentages of correct, incorrect and late responses were entered into repeated measures general linear models (GLMs) with the between factor Group (patients vs. controls) and the possible within-subjects factors of Congruency (congruent vs. incongruent) and Correctness (correct vs. incorrect) and BDI-II scores as a covariate.

To investigate behavioral adjustments following internal performance monitoring, the amount of post-error slowing (Rabbit 1966) was investigated. Post-error slowing was defined as the difference in RT between correct responses

following incorrect responses and correct responses following correct ones (see e.g. Schrijvers et al., 2008). Post-error adjustments were analyzed in repeated measures GLMs with the between-subjects factor Group (patients vs. controls) and the within subjects factor Post-Correctness (post-error vs. post-correct) and BDI-II scores as a covariate.

Electrophysiological data analyses

EEG analyses were conducted using Brain Vision Analyzer 2.0. All electrodes were originally referenced to the ground electrode (placed at AFz) and the reference electrode (placed between Cz and Pz) but were later off line re-referenced to the average of T7 and T8. Eye movements were recorded with the vertical electro-oculogram (EOG) from electrodes that were placed above and below the right eye and the horizontal EOG from electrodes placed lateral to both eyes. The EEG and EOG signals were amplified using a band-pass filter between .02 Hz and 15 Hz and digitized at 250 Hz.

The EEG was corrected for EOG artifacts using an ocular correction with independent component analysis (Gratton et al., 1983). For the ERN analysis, ERPs were time-locked to response onset and averaged separately for correct and incorrect responses relative to a 200 msec pre-response baseline. ERN amplitude was determined on correct and incorrect responses by calculating the differences between the most negative peak in the 0-150 msec time window after response onset and the most positive peak in the time window starting 80 msec before and ending 80 msec after response onset at electrode FCz where maximal ERN amplitudes were expected (see e.g. Falkenstein et al., 2000; Ullsperger and von Cramon 2001; Bates et al., 2005). N1, N2 and P3 amplitudes were determined on correct stimulus-locked ERP's as the most negative peak in the 0-150 msec time window (N1), 200-350 msec time window (N2) at electrode FCz and the most positive

peak in the 300-800 msec time window (P3) at electrode Pz where maximal amplitudes were expected (Franken et al., 2007).

Statistical analyses were performed using SPSS 20. The ERN was analyzed in a repeated measures GLM using Group (bipolar vs. control) as the between subjects factor and Correctness (correct vs. incorrect response) as the within subjects factor and BDI-II as a covariate. N1, N2 and P3 components were analyzed in a repeated measures GLM using Group (bipolar vs. control) as the between subjects factor and Congruency (congruent vs. incongruent) as the within subjects factor and BDI-II as a covariate.

Results

Demographic and clinical rating scales

Based on a low error rate (<10 errors), 3 patients and 5 controls were excluded from all analyses leaving 16 patients (10 male, mean age 47.25 years, SD=10.7) and 14 healthy controls (5 male, mean age 43.5, SD=15.7). For an overview of the demographic and clinical characteristics, see Table 1.

There were no statistically significant differences in the groups regarding age, education and gender. While the YMRS and HDRS were not high enough to classify the patients as clinically depressed or manic, the scores of the euthymic patients did differ significantly from the healthy controls with higher scores on both measures (YMRS: $t(28)=2.33$, $p=.05$; HDRS: $t(28)=3.58$, $p=.006$), indicating possible residual mood symptoms present in the BD patients. In addition, the specific assessment of residual depressive symptoms by means of the self-reported BDI-II questionnaire showed that patients had significantly higher BDI-II scores than the control group ($t(28)=2.58$, $p=.004$). Statistically controlling for current mood symptoms can cause significant differences between groups to disappear (Clark and Iversen 2002; Ferrier et al., 1999). Therefore, the influence of residual depressive symptoms on

performance needs to be controlled for and all further analyses were conducted using ANCOVA with BDI-II scores as a covariate.

Table 1: Overview of demographic and clinical characteristics

	Bipolar disorder (n=16)	Control (n=14)
Gender	62.5% Male	42.8% Male
Age, mean years (SD)	47 (10.65)	43 (15.74)
Education level (SD)	1.875 (0.81)	2.142 (0.66)
Clinical rating scale, mean, (SD)		
YMRS	2.312 (2.06)	0.714 (1.64)*
HDRS	3.25 (2.59)	0.71 (1.14)**
BDI-II	11.062 (9.66)	3.928 (3.92)*

*p<.05 **p<.01, YMRS=Young Mania Rating Scale (Young et al, 1978), HDRS=Hamilton Depression Rating Scale (Hamilton, 1960), BDI-II= Beck Depression Inventory (Beck et al, 1996). Education level subdivided in a low (1), medium (2) and high (3) level in accordance with the Belgium education system.

Behavioral results

Reaction times

Analysis of correct responses only yielded a main effect of Congruency, indicating that both patients and controls responded slower to incongruent stimuli (479 msec) than to congruent stimuli (443 msec) ($F[1,27]=11.04$, $p=.003$). There was

no main effect of Group nor were there significant interactions between Congruency and Group (both Fs<1) or Congruency and BDI-II (F[1,27]=1.07, p=.31).

When incorrect responses were included in the analysis, there was no longer a significant main effect of Congruency (F[1,27]=1.66, p=.21). There was also no significant main effect of Group or BDI-II (both Fs<1). However, there was a significant main effect of Correctness (F[1,27]=6.06, p.02). Subjects responded faster when they were incorrect (429 msec) than when they were correct (460 msec). In addition, there was also a significant interaction between Congruency and Correctness (F[1,27]=15.65, p<.001) suggesting that subjects responded much faster to congruent stimuli (442 msec) than to incongruent stimuli (478 msec) when the responses were correct (t(29)=-3.63, p=.001), while the RT of incorrect responses were generally fast for both congruent and incongruent stimuli (429 vs. 430 msec respectively; t(29)=-1.2, p=.91) (see Table 2).

Differential response time limits were used to impose consistent accuracy across participants. Analysis of the response time limits did not yield a significant main effect of Group (F<1) suggesting that a similar response time limit was employed in both the patients (599 msce) and the controls (621 msec).

Table 2: Mean reaction times in milliseconds (standard deviations in parentheses) of correct and incorrect responses of the bipolar disorder patients and controls to congruent and incongruent stimuli

	Bipolar disorder		Control	
	Congruent	Incongruent	Congruent	Incongruent
Incorrect	481.02 (84)	423.44 (133)	439.30 (69)	436.94 (63)
Correct	449.91 (61)	476.39 (103)	434.80 (44)	481.02 (47)

Error and late responses

Table 3 provides an overview of the mean percentages of correct, incorrect and late responses for the two groups. When looking at error rates, no main effect was found for Group ($F[1,27]=1.77$, $p=1.94$) or BDI-II ($F<1$), however there was a significant main effect of Congruency ($F[1,27]=34.27$, $p<.001$), with subjects in both groups making more errors on incongruent trials (5.1%) than on congruent ones (2%). The interactions between Congruency and Group and between Congruency and BDI-II were not significant (Fs<1).

The analysis of late responses also had a significant main effect of Congruency [$F(1,27)=23.93$, $p=<001$]. Incongruent trials resulted in more late responses (8.4%) than congruent trials (3.9%). There was no main effect of Group or of BDI-II nor were there significant interactions between Congruency and Group ($F<1$) or Congruency and BDI-II (all Fs<1).

Table 3: Mean percentage (standard deviations in parentheses) for incorrect, correct and late responses. Values are present for the bipolar disorder patients and controls for congruent and incongruent stimuli

	Bipolar disorder		Control	
	Congruent	Incongruent	Congruent	Incongruent
Incorrect	2.6 (.03)	5.8 (.03)	1.3 (.01)	4.4(.02)
Correct	42.7 (.05)	35 (.05)	46.0 (.02)	37.2 (.05)
Late	4.5 (.05)	9.2 (.06)	3.3 (.01)	7.7(.03)

Behavioral adjustments following performance monitoring

For performance monitoring, Post-error and Post-correct responses were compared. There was a significant main effect of Post-Correctness ($F[1,27]=42.48$, $p<.001$). Correct responses following errors were slower (533 msec) than correct responses following correct responses (477 msec). This reflects behavioral adjustment known as post-error slowing (Eriksen and Eriksen 1974). The interactions between Post-error and Group and between Post-error and BDI-II were not significant ($Fs<1$) indicating that both the patients and controls manifested the same amount of Post-error slowing. There were also no main effects of Group or BDI ($Fs<1$).

Response-locked ERP analyses

Figure 1 illustrates the ERP amplitudes at electrode FCz for patients and controls.

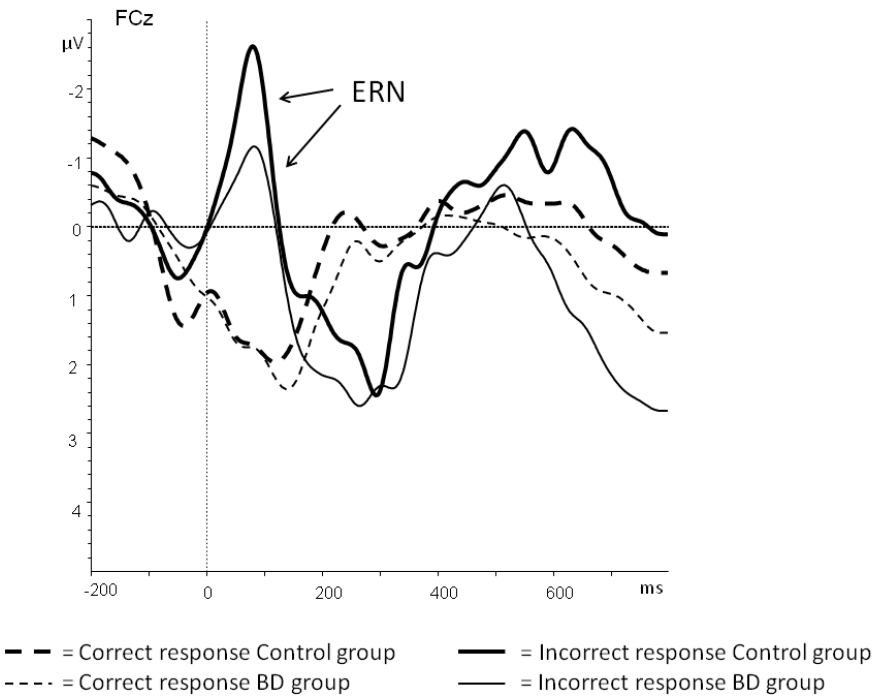

Figure 1: Grand average response-locked waveforms for correct (dashed lines) and incorrect (solid lines) responses for both the control (thick lines) and BD group (thin lines). Electrode FCz is depicted. Response onset is at time=0 msec.

The analysis of ERP including BDI-II scores as a covariate revealed a significant main effect of Correctness ($F[1,27]=8.563$, $p=.007$), demonstrating the expected pattern of more negative amplitudes for incorrect responses (-4.73 μV) than for correct ones (-1.44 μV). There was no main effect of Group ($F[1,27]=1.24$, $p=.28$), or BDI-II ($F<1$). However, there was a significant interaction between Correctness and

Group. The negative ERN effect for incorrect responses compared with correct responses was greater in the control group (-3.98 μV difference) than in the bipolar disorder group (-2.53 μV difference) (F[1,27]=4.629, p=.041).

Table 4 illustrates the ERN amplitudes for correct and incorrect responses in the different groups when controlling for the BDI-II scores compared with not controlling for BDI-II scores. Importantly, taking the differences of BDI-II scores into consideration, there was a larger difference between correct and incorrect responses in the control group than in the bipolar disorder group, while there were no group differences when the covariate BDI-II was excluded from the analysis (F[1,28]=1.78, p=.40)[1].

Table 4: Mean values (standard deviations in parentheses) for response-locked peak-to-peak values (in microvolts) for the error related negativity (ERN) on correct and incorrect trials. All values are presented for both the patients and the controls with and without the BDI-II scores as a covariate.

	No covariate		BDI-II covariate	
	Bipolar disorder	Control	Bipolar disorder	Control
Incorrect	-3.96 (.88)	-5.44 (.94)	-3.55 (.92)	-5.9(.96)
Correct	-1.43 (.49)	-1.45 (.52)	-1.51 (.52)	-1.37 (.56)

[1]Patients also scored higher on the clinical rating scales (YMRS and HDRS) than controls and these may have had an effect on the ERN amplitudes. An ERN analysis including YMRS, HDRS and BDI-II scores as covariates simultaneously did not reveal any significant influences on group. There were no significant main effects of
Group, BDI-II, YMRS or HDRS. However there was a significant interaction between the BDI-II scores and Correctness (F[1,25]=4.72, p=.039) confirming that there is a specific effect of BDI-II scores on ERN amplitudes.

Stimulus-locked ERP analyses

Analyses of N1, N2 and P3 also included BDI-II scores as a covariate. N1 analysis showed no significant main effects of Congruency, Group or BDI-II (all Fs<1). Neither was there a significant interaction between Congruency and Group (F[1,27]=1.43, p=.24). Similarly, N2 analyses did not yield significant main effects of Congruency, Group or BDI-II (all Fs<1) nor a significant interaction between Congruency and Group (F<1).

P3 analyses revealed a significant main effect of Group (F[1,27]=6.95, p=.01). Control subjects showed a larger P3 peak for both congruent and incongruent stimuli (7.15 μV) than bipolar disorder patients (3.15 μV). There was no significant main effect of Congruency or BDI-II (both Fs<1), nor was there a significant interaction between Congruency and Group (F[1,27]=1.766, p=.20).

Analyses of potential confounding factors:

Medication

A potential confounding factor is the different medications that the patients were on. Medications (benzodiazepines, antipsychotics and antidepressants) were coded as 'on' or 'off' for each subject. Adding their medications as an additional between subjects factor, the analysis showed only a significant effect of Correctness (F[1,22]=9.98, p=.005). There was no significant main effect of Group (F<1), nor was there a significant interaction between Correctness and Group (F<1). There were no significant main effects of medication use (all Fs<1) nor were there any significant interactions between medication use and Correctness (all Fs<1)[2].

[2] An ERN analysis using Location as a between subjects factor was conducted to ensure that the location of measurement did not influence the results and were not a source of group differences. There was no significant main effect of Location (F[1,24]=1.47, p=.25).

History of psychosis

It is also possible that history of psychosis influenced the results. Therefore, psychotic history (coded as 'on' or 'off') was analyzed by adding Psychosis as an additional between subjects factor. Results revealed a significant main effect of Correctness ($F[1,27]=30.42$, $p<.001$). There was no significant main effect of Group ($F[1,27]=1.33$, $p=.258$), nor was there a significant interaction between Correctness and Group ($F<1$). There was no significant main effect of Psychosis nor was there a significant interaction between Psychosis and Correctness (both $Fs<1$).

Discussion

The current study was the first study to investigate performance monitoring using the ERN in patients with bipolar disorder in a euthymic state compared to a matched control group. The results showed decreased performance monitoring in patients with bipolar disorder, in support of the hypothesis, however, these results were only present when taking residual mood symptoms into account. There were lower ERN amplitudes, signals of error detection in the bipolar disorder group compared with healthy controls, indicating less activation in the ACC when errors were made, a critical element of performance monitoring (van Veen and Carter 2006; Kerns et al., 200). An impaired ability to dissociate between correct and incorrect responses was also found in bipolar disorder, an additional effect of impaired performance monitoring (Spronk et al., 2011).

Results of this study are in line with previous state theories of ERN (Bates et al., 2004; Schrijvers et al., 2008). Patients in a euthymic state have residual mood alterations, as shown in higher depression rating scores (BDI-II). In addition, it is known that depression scores, especially mild to moderate depression scores may affect ERN amplitudes. Therefore, it was essential to take into account depressive state in the analysis in order to detect influences on the ERN. Controlling for

differences in self-reported depressive symptoms showed that patients with BD had lower ERN amplitudes compared with controls. These ERN group differences were no longer present when depressive symptoms were not controlled for. In other words, patients with BD show lower ERN amplitudes compared with healthy controls but residual depression symptoms may have raised the ERN amplitudes to the extent that abnormally low ERN amplitudes were no longer visible. Therefore, as in previous studies on mild depression (Elliott 1998; Holmes and Pizzagalli 2008; Chiu and Deldin 2007) this study confirms that clinical state may influence ERN amplitudes with mild depressive symptoms resulting in higher ERN amplitudes.

The findings of this study are also in line with previous trait theories of decreased ERN in psychotic disorders (Olvet and Hajcak 2008). Results revealed lower ERN amplitudes in euthymic bipolar disorder after controlling for clinical variables. This indicates that patients with bipolar disorder are impaired in performance monitoring, regardless of mood state, indicating that decreased ERN may be related to the bipolar pathophysiology and thus broadening the cognitive profile to include not only lower level cognitive deficits (Bearden et al., 2001), but higher order cognitive deficits as well. In addition, although history of psychosis has been shown to have a possible effect on the ERN (Minzenberg et al., 2014; Foti et al., 2012), the decreased ERN amplitudes found in this study were independent of psychosis. BD is a psychotic disorder and shares a similar cognitive profile with schizophrenia, BD patients in a euthymic state (with and without a history of psychosis) appear to have similar decreased ERN patterns as schizophrenic patients (Debener et al., 2005; De Bruijn and Ullsperger 2011; Alain et al., 2002; Bates et al., 2002; Bates et al., 2004; Houthoofd et al., 2013; Kim et al., 2006), further supporting the theory of a general failure of internal monitoring of errors in psychotic disorders (Olvet and Hajcak 2008).

It is possible that ERN findings are influenced by deficits in early perceptual processes, reflected in the stimulus-locked N1 or in later attentional processes reflected in the stimulus-locked N2 and P3. Importantly, no differences in the N1 and

N2 components were found. However, BD patients had lower P3 amplitudes compared with controls. Previous studies investigating P3 in BD using a different attentional paradigm, an oddball task, yielded mixed results. While reduced P3 amplitudes in BD has been demonstrated (Bestelmeyer et al., 2009), other studies did not find any P3 differences in BD (Lahera et al., 2009; Bestelmeyer et al., 2012). It is difficult to compare this study with previous results as the Flankers task used here is not sensitive to measure changes in P3. Although the currently found reduced P3 amplitudes might reflect reduced late attentional processing of the stimulus, this interpretation seems unlikely as there were no behavioral group differences. In other words, the currently found reduction of ERN amplitudes in BD compared with controls cannot simply be a reflection of a general impairment in cognitive processing in BD.

Behavioral results in the current study showed similar reaction times, error rates and post-error slowing (Rabbit 1966) in the bipolar disorder group and the healthy controls. Both groups responded slower for incongruent stimuli, faster when the response was incorrect and slowed down following an error. These results indicate that patients with BD in a euthymic state have normal responses to error commission. In contrast to normal behavioral findings of performance monitoring, patients showed decreased error-related neural activations representing a decreased internal response to making an error. While many studies fail to find a connection between behavior and the ERN amplitudes (e.g. De Bruijn et al., 2004; Ullsperger et al., Ullsperger and von Cramon 2006), this is possibly due to the very strict RT deadline employed in this flankers task. Individually determined RT deadlines (used in order to ensure similar performance levels between the groups) results in a limited time that participants can respond correctly, making it difficult to respond significantly slower following an error. Therefore, the absence of performance effects in this study is likely due to these individualized deadlines.

Our findings also add to previous studies reporting conflicting evidence regarding the specific role of the ACC in bipolar disorder (Gruber et al., 2004;

Blumberg et al., 2003; Strakowski et al., 2005). Our design enabled us to use electrophysiology to measure performance-monitoring processes and error-related activity generated in the ACC. The divergent findings of the ACC in BD to date could be the result of not taking into account residual mood symptoms in euthymic patients. Subclinical features, specifically subthreshold depression (BDI-II scores) should be taken into account (Martinez-Aran et al., 2000; Kessing 1998; Fava 1999) as even small differences may lead to different error-related ACC activations.

The findings should be considered in light of the limitations of the study. Firstly, a relatively small sample size was used in this experiment. Secondly, it is known that ERN amplitudes may be modulated by medication (De Bruijn et al., 2004; De Bruijn et al., 2006b; Zirnheld et al., 2004). However, it is unlikely that this affected our data as additional analyses demonstrated similar results when controlling for medication status. While age, education, gender, medication and other clinical variables were controlled for and were not found to affect the results in any way, it is possible that just as subthreshold depression influenced the results, other variables in bipolar disorder may also have played a role such as number of mood episodes and duration of illness. This highlights the difficulty in testing cognition in bipolar disorder. A further limitation of the study is that ERN abnormalities may be the result of a cognitive deficit (abnormal error detection), an affective deficit (abnormal affective evaluation during error detection) or both. In the search for cognitive deficits in BD, it is essential to separate any emotional deficits that may interact with the cognitive deficits. Therefore, future studies could combine both cognitive and affective neuroscience in the analysis of the ERN in BD by directly manipulating emotion processing during a cognitive task. This could allow more insights into the ERN patterns, specifically whether the ERN abnormalities in BD are due to abnormal emotion processing, or whether *despite* their abnormal emotion processing, there are additional ERN abnormalities.

Conclusion

Patients with BD in a euthymic state have decreased ERN amplitudes compared with healthy controls when controlling for subjectively rated residual mood symptoms, indicating an impaired performance-monitoring system. The clinical implication of impaired performance monitoring is that patients with BD may experience problems in flexibly adjusting their behavior. This is essential for goal-directed behavior and problems in this regard may importantly interfere with treatment compliance. This study also highlights state influences on the ERN patterns in bipolar disorder as well as a possible underlying pathological ERN impairment in psychotic disorders.

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Chapter 6

An overview of pharmacotherapy for bipolar I disorder

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Abstract

Introduction

Bipolar I disorder (BD) is complex with a chronic course that significantly impacts a sufferer's quality of life. As of right now, there are many available treatments that aim to rapidly treat manic or depressive episodes and stabilize mood**.** The purpose of this report is to provide an up-to-date comprehensive review of the available evidence-based trials of pharmacotherapy for the treatment of BD I.

Areas covered

This paper reviews randomized active comparator-controlled or placebo-controlled trials evaluating the use of current pharmacotherapy in adults with BD I from phase III to clinical practice.

Expert opinion

There are many treatments available for BD mania; however, the depressive and stabilization phases of the illness remain a clinical challenge. Unfortunately, randomized controlled trials do not represent 'real world' patients, as their strict inclusion and exclusion criteria do not allow for different features sometimes present in patients to be considered. Research efforts must also focus on treating cognitive deficits, which adds to lower functional outcome. The authors believe that there is dire need for new, more targeted treatments in BD I, with a critical view of the side effects.

Introduction

Bipolar I disorder (BD) is characterized by the occurrence of at least one acutely manic or mixed feature episode (where both manic and depressive features are present) in addition to major depressive episodes and periods of relative euthymia. According to the 5th edition of the Diagnostic and Statistical Manual of Mental disorders (DSM), major depressive episodes are not necessary for a diagnosis of BD I (APA 2013). Previous criteria for a manic episode was based solely on elevated mood (DSM-IV), but has been revised to include and require changes in activity and energy as well (DSM-5). BD includes additional symptoms and comorbidities such as psychotic symptoms, cognitive impairment, anxiety disorders and/or substance abuse disorders (Sachs et al., 2011a). Although the classic description of BD is of cyclical nature, recent evidence suggests that BD has a more chronic course with residual symptoms (especially depression) and cognitive impairments persisting in between major mood episodes Leboyer and Kupfer 2010). However, when psychotic symptoms are present during euthymia (in addition to a BD history), a diagnosis of schizoaffective disorder needs to be considered as opposed to BD I. BD I has an estimated prevalence affecting approximately 1% of the population (Merinkagas et al., 2007) and significantly impacts quality of life, with evidence of poor occupational and social functioning (Fagiolini et al., 2013).

Approximately half of the individuals with BD I have a course of illness that is characterized by either predominant manic symptoms or predominant depressive symptoms, and is referred to as predominant polarity Colom et al., 2006). Patients with manic polarity show more frequent substance misuse, psychotic symptoms, and cognitive impairments (Colom et al., 2006; Martinez-Aran et al., 2007) while patients with depressive polarity have more suicide attempts (Rosa et al., 2008). A large proportion of patients with BD I have rapid cycling (14-53%), which is a clinically specific course of the illness defined as more than four mood episodes in a year (Tondo and Baldessarini 1998).

Despite the fact that the occurrence of mania is a defining feature of BD I, depressive episodes in BD are in fact much more common (Judd et al., 2002) to the extent that individuals with BD spend a large proportion of their lives in a depressed state (Judd and Akiskal 2003). Nevertheless the majority of pharmacological studies have focused on drugs treating mania. Acute mania is often a medical emergency and the treatment objective is to control symptoms of agitation, aggression or dangerous behavior as quickly as possible so that psychosocial functioning can return to normal.

Current treatment strategies are targeted towards rapidly treating acute manic or depressive episodes and stabilizing mood. Stabilization includes preventing relapse of a mood episode or reducing the frequency of episodes or the severity of symptoms (and subthreshold symptoms) in order to enhance social and occupational functioning. The most recently updated guidelines are the National Institute for Health and Care Excellence (NICE) guidance for bipolar disorder (Goodwin et al., 2016) and the British Association of Psychopharmacology (BAP) guidelines for treating bipolar disorder(Kendall et al., 2013). These guidelines recommend antipsychotic treatment for mania, if not already taking a mood stabilizing drug. If a patient is currently taking a mood stabilizer, an antipsychotic should be added. First line treatment options for BD depression include quetiapine or the combination of olanzapine and fluoxetine. Long term maintenance therapy should take into account the drug that worked during the acute treatment stage. However, treatment remains a challenge due to the complexities of BD. A large range of factors need to be considered when choosing between treatment options such as the phase of the illness (acute episode or maintenance), symptoms (mania or depression), rapid cycling, polarity, psychiatric and somatic co-morbidities and psychotic and cognitive symptoms. In addition, side effects of medications need to be considered, as drug tolerance which typically is a challenge with mood stabilizing drugs, has a large impact on treatment adherence (Bates et al., 2010).

Treatment strategies, treatment guidelines and diagnostic criteria have been shifting over the years for BD. Therefore the purpose of the current review is to

provide an updated comprehensive review and evaluation of the available evidence-based trials of pharmacotherapy for the treatments of BD I.

Methodology

We conducted a MEDLINE search (via Pub Med database) to identify randomized active comparator-controlled or placebo-controlled trials (RCTs) evaluating the use of current pharmacotherapy in BD I as monotherapy or in combination therapy for acute and long-term treatment. The terms bipolar disorder/ bipolar depression/ bipolar mania were combined with treatment or one of the following: mood stabilizer, anticonvulsants, antiepileptics, antipsychotics, and antidepressants. In addition, the terms were combined with individual drugs: lithium, valprorate/ divalproex/ valproic acid/ divalproate, carbamazepine, oxcarbamazepine, gabapentin, aripiprazole, risperidone, olanzapine, ziprasidone, quetiapine, asenapine, paliperidone, lamotrigine, topiramate, haloperidol, lurasidone, clozapine, cariprazine, paroxetine, fluoxetine, sertraline, citalopram, escitalopram, bupropion, venlafaxine, imipramine, agomelatine, modafinil, armodafinil, inositol, tamoxifen.

Studies were identified from searches up to May 2017. This search was supplemented by manually reviewing reference lists from publications and when appropriate, information from meta-analyses and systematic reviews were also considered. Studies conducted in children and adolescents and studies prior to phase III were excluded. In total, 119 RCTs satisfied the inclusion criteria. There were 69 studies for acute mania (47 monotherapy trials and 22 combination trials), 28 relating to acute depression (15 monotherapy trials and 13 combination trials) and 22 maintenance studies.

Treatment of acute mania

Monotherapy

Evidence from early studies (Boden et al., 1994; Freeman et al., 1992; Pope et al., 1991) demonstrated that both lithium and valproate were effective as monotherapy in treating manic symptoms. This was confirmed by more recently conducted studies (Bowden et al., 2005; Bowden et al., 2006; Keck et al., 2009; Kushner et al., 2006; Tohen et al., 2008a), with the exception of one (Hirschfeld et al., 2010). However, lithium has several common side effects including tremor, thirst and weight gain (Dunner 1999). In addition, lithium has a very narrow therapeutic index with potential to produce toxicity at doses not much greater than what is required in order to have therapeutic effect (Freeman and Freeman 2006), making regular lithium level monitoring necessary. The target range for serum lithium is 0.6 to 0.8 mmol/litre (Boon 2016). Valproate is also associated with adverse effects including gastrointestinal disturbances, tremor, sedation and weight gain (APA 2002; Perucca et al., 2002). The suggested target range for plasma concentrations for mood stabilization is 50-100 mg/litre. plasmatic range (Boon 2016).

Carbamazepine has also been shown to reduce manic symptoms (Small et al., 1991; Weisler et al., 2004; Weisler et al., 2005), however compared with valproate, carbamazepine was slower to reduce symptoms and less well tolerated (Vasudev et al., 2000). Both valproate and carbamazepine are associated with neural tube defects and should be administered with caution with women who wish to become pregnant (Connolly and Thase 2011). In addition, carbamazepine induces cytochrome P450 enzymes which leads to increased breakdown of other pharmacological agents (including mood stabilizers, antiepileptics and antidepressants). As a result of these potential complex drug interactions, carbamazepine should be administered with caution when combining with other drugs. The target range for serum carbamazepine is 7 -12 mg/litre (Boon 2016). Oxcarbamazepine was equally

effective as valproate and had less side effects (Kakkar et al., 2009). Although topiramate is sometimes used to treat BD, evidence from a single study does not support its use as monotherapy for BD mania (Kushner et al., 2006). Topiramate did not differentiate from placebo and there were many side effects including appetite decrease, paresthesia, dry mouth and weight loss (Kushner et al., 2006).

Earlier guidelines promoted lithium and valproate as first line treatment of acute mania, however more recently, antipsychotics have been gaining terrain. Evidence based guidelines for the treatment of BD I, such as the American Psychiatric Association (APA 2002), BAP (Goodwin et al., 2016), International Society for Bipolar Disorders (Yatham et al., 2009) and NICE (Kendall et al., 2014) recommend that in addition to lithium, second generation antipsychotics are an appropriate first line of treatment based on evidence of rapid anti-manic efficacy and less side effects (see Nivoli et al., 2011 for review of guidelines).

Studies comparing second generation antipsychotics with a placebo or an active comparator such as lithium have demonstrated reduced manic symptoms at 3 or 4 weeks with risperidone (Hirschfeld et al., 2004; Khanna et al., 2005; Segal et al., 1998; Smulevich et al., 2005), ziprasidone (Keck et al., 2003a; Potkin et al., 2005; Vieta et al., 2010a), quetiapine (Bowden et al., 2005; Cutler et al., 2011; Li et al. 2008; McIntyre et al., 2005; Vieta et al. 2010b;), paliperidone (minimum 12 mg/d) (Berwaerts et al., 2012; Vieta et al., 2010b), and aripiprazole (Kanba et al., 2014; Keck et al., 2003b; Keck et al., 2009; Sachs et al., 2006; Young et al., 2009) (except for one study, (El Mallakh et al., 201), which had a high placebo response rate). Manic symptoms were also reduced in phase III trials of asenapine (Landbloom et al., 2016; McIntyre et al., 2009; McIntyre et al., 2010) and cariprazine (Calabrese et al., 2014a; Sachs et al., 2015). Symptoms were found to be reduced very rapidly (within days) and were relatively well tolerated (Hirschfeld et al., 2010; Keck et al., 2003a; Keck et al., 2003b; Keck et al., 2009; Khanna et al., 2005; McIntyre et al., 2009; McIntyre et al., 2010; Potkin et al., 2005; Sachs et al., 2006; Vieta et al., 2010b; Young et al., 2009). While olanzapine also reduced manic symptoms (Berk et al., 1999; Katagiri et

al., 2012; McIntyre et al., 2009; Niufan et al., 2008; Perlis et al., 2006; Shafti et al., 2010; Tohen et al., 1999; Tohen et al., 2000; Tohen et al., 2003a; Tohen et al., 2008a; Zajecka et al., 2002), there were consistently more metabolic adverse events with olanzapine compared with lithium.

Haloperidol, a first generation antipsychotic, reduced manic symptoms very rapidly, however there were consistent findings of adverse motor side effects (Katagiri et al., 2012; McIntyre et al., 2005; Segal et al., 1998; Smulevich et al., 2005; Vieta et al., 2005; Vieta et al., 2010a; Young et al., 2009). Tamoxifen reduced manic symptoms and was well tolerated (Yildiz et al., 2008). For a summary of important variables of each study assessing drugs as monotherapy for acute mania, see Table 1.

Combination therapy

Adjunctive asenapine, aripiprazole, risperidone, haloperidol, allopurinol (600 mg/d and not 300 mg/d) and tamoxifen to a mood stabilizer demonstrated rapid superior efficacy compared with mood stabilizer monotherapy (Amrollahi et al., 2011; Garfinkel et al., 1980; Jahangard et al., 2014; Machado-Vieira et al., 2008; Sachs et al., 2002; Szegedi et al., 2012; Vieta et al., 2008a; Weiser et al., 2014; Yatham et al., 2003) with relatively high tolerability. As high doses of haloperidol have many adverse side effects, it was found that adding lithium or valproate to a lower dose of haloperidol enhanced the efficacy of haloperidol while reducing side effects (Chou et al., 1999), making it more effective than both mood stabilizer monotherapy and haloperidol monotherapy.

Although the addition of ziprasidone to a mood stabilizer had no advantage over mood stabilizer monotherapy at 3 weeks (Sachs et al., 2012), it was observed that adjunctive ziprasidone reduced symptoms at day 4 (Weisler et al., 2003), suggesting that the addition of ziprasidone may be useful for rapid reduction of symptoms. Similarly, adjunctive risperidone was faster to begin taking efficacy compared with risperidone monotherapy (Moosavi et al., 2014).

Results related to adjunctive quetiapine for bipolar mania are unclear with studies demonstrating greater efficacy than a mood stabilizer alone (Sachs et al., 2004) or quetiapine monotherapy (Bourin et al., 2014) and another study failing to show superior efficacy Yatham et al., 2007).

Olanzapine combined with lithium or valproate was more effective in reducing manic symptoms compared to monotherapy with a mood stabilizer or olanzapine (Tohen et al., 2002; Xu et al., 2015) but there were more adverse events including weight gain, slurred speech and tremor (Tohen et al., 2002). Combining olanzapine with carbamazepine was not more effective than carbamazepine monotherapy and there was more weight gain (Tohen et al., 2008b). These studies suggest that olanzapine is not optimal for adjunctive therapy. Similarly, combining paliperidone or topiramate to a mood stabilizer did not add any benefits (Berwaerts et al., 2011; Roy et al., 2006) and both had more adverse events such as insomnia (Berwaerts et al., 2011) or weight gain (Roy et al., 2006).

Adjunctive gabapentin to a mood stabilizer was worse than mood stabilizer monotherapy (Pande et al., 2010). Table 2 provides an overview of important variables in the studies investigating combination therapy in mania.

Discussion

The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved lithium, valproate, carbamazepine and most second generation antipsychotic monotherapy for the treatment of mania, although the EMA only recommend valproate when lithium is not tolerated (Wang et al., 2010). Evidence from RCTs show that lithium and valproate are effective as are the antipsychotics risperidone, ziprasidone, quetiapine, paliperidone, aripiprazole and asenapine. Both olanzapine and haloperidol are effective but have more side effects. Recently approved guidelines (BAP, NICE) also recommend combination therapy of a

second generation antipsychotic with lithium or valproate when symptoms are more severe and do not respond to monotherapy (Goodwin et al., 2016; Kendall et al., 2014), although increasing medications add more adverse side effects (Scherk et al., 2007). Results of RCT combination studies demonstrated efficacy in reducing manic symptoms by combining allopurinol, asenapine, aripiprasole, risperidone, possibly quetiapine and low doses of haloperidol with a mood stabilizer. As in monotherapy trials, the addition of olanzapine adds adverse events and should be administered with more caution.

As a result of motor side effects, haloperidol is classically viewed as being less well tolerated than second generation antipsychotics and lithium. However, other second generation antipsychotics demonstrate more metabolic side effects including weight gain (up to 20-30 kg), diabetes and hypercholesterolemia and as a result (due to cardiovascular comorbidity) can lead to higher mortality (Correll et al., 2006). Specifically, there is evidence from studies investigating olanzapine demonstrating these side effects (Berk et al., 1999; Katagiri et al., 2012; McIntyre et al., 2009; Niufan et al., 2008; Perlis et al., 2006; Shafti et al., 2010; Tohen et al., 1999; Tohen et al., 2000; Tohen et al., 2003; Tohen et al., 2008a; Zajecka et al., 2002). In addition, as mentioned above, lithium has important side effects including strong neural side effects when concentrations are too high which may be fatal. While lithium, valproate and carbamazepine require blood monitoring, second generation antipsychotics do not. This highlights the importance of taking in to account drug tolerability in the assessment of drug efficacy.

Interestingly, a recent meta-analysis attempting to compare efficacy and tolerability of antimanic drugs during the acute manic phase (Cipriani et al., 2011) demonstrated that antipsychotics were better overall than mood stabilizers, the best being olanzapine, haloperidol and risperidone. This is not completely in line with evidence presented in this review which demonstrated more side effects with olanzapine and haloperidol. This difference may possibly result from the tolerability criteria used in the meta-analysis, which was the drop-out rate at 3 weeks. As many

symptoms appear at a later stage, results of the meta-analysis should be interpreted with caution (Berk and Malhi 2011). Moreover, although lithium acts slower than second generation antipsychotics and may be seen as less successful for treatment of acute episodes, it clearly has long term benefits, with evidence of reduced risk of relapse of mania and depression (Geddes et al., 2004) and decreased risk of suicide (Baldessarini et al., 2008).

Treatment of acute depression

Monotherapy

Table 3 summarizes data from studies investigating drugs as monotherapy for BD I depression. Unfortunately, there is relatively little data relating to pharmacotherapy in BD depression and all recently updated guidelines (Fountoulakis et al., 2016; Goodwin et al., 20016; Grunze et al., 2013; Kendall et al., 2014; Yatham et al., 2009;) concur that more research in this area is needed. Current evidence does not support lithium monotherapy during the depressive phase (Young et al., 2010), with lithium having equal efficacy as a placebo. A few studies have investigated anticonvulsants in BD depression. Two very small studies demonstrated that valproate is effective in the reduction of depressive symptoms (Davis et al., 2005; Muzina et al., 2011). However, the efficacy of valproate for bipolar depression needs to be interpreted with caution due to the small number of participants in each group (12-25 subjects).

While clinically lamotrigine appears to demonstrate benefits following treatment (Weisler et al., 2008), evidence from RCTs supporting this has been weak. One early study found that lamotrigine reduced depressive symptoms at 3 weeks (Calabrese et al., 1999). Results of a later study (including 5 trials, 3 of them specifically related to BD I) failed to differentiate statistically any benefits from lamotrigine compared to placebo (Calabrese et al., 2008). Pooled data analysis of

these studies found an overall modest benefit of lamotrigine, which was not present in individual analyses (Geddes et al., 2009). It is important to note that the most common adverse event leading to discontinuation of lamotrigine is a rash, which may in rare cases (0.3% of the population) lead to the serious consequence of Steven Johnson syndrome, a life threatening dermatological condition (Lamitcal product information, 2001). In order to avoid this risk, the dose of lamotrigine has to be increased very slowly often leading to 6-8 weeks before reaching an optimal dose, which is too long for acute management. The suggested target range for plasma concentrations for mood stabilization is 2.5-15 mg/litre (Boon 2016). In other words, lamotrigine may be suitable for acute treatment of the depressive episodes in BD but more evidence is necessary. There are no randomized controlled studies investigating the efficacy of carbamazepine or topiramate in BD I depression.

Quetiapine (300 and 600 mg/d) is the most extensively studied second generation antipsychotic in BD depression. Studies comparing it to placebo demonstrated a reduction in depressive symptoms at either dose (Calabrese et al., 2005a; McElroy et al., 2010; Suppes et al., 2014; Thase et al., 2006; Young et al., 2010), with effects beginning from the first week (Calabrese et al., 2005a; Suppes et al., 2014). Additionally, quetiapine was found to have greater efficacy for BD depression compared with lithium (Young et al., 2010) with high tolerability. Lurasidone was also found to be effective in BD depression (Loebel et al., 2014a) compared with placebo. Similar to BD mania, studies investigating olanzapine in BD depression have demonstrated efficacy in reducing symptoms (Tohen et al., 2003b; Tohen et al., 2012; Wang et al., 2014), however metabolic side effects were common.

Neither aripiprazole nor ziprasidone were effective in reducing depressive symptoms (Lombardo et al., 2012;Thase et al., 2008) compared with placebo. Although aripiprazole reduced depressive symptoms initially (by week 5-6), by the 8th week, aripiprazole was comparable to placebo. In addition, it was not well tolerated with side effects including acathisia, insomnia, nausea, fatigue, restlessness, and dry mouth. There have been no randomized controlled studies investigating risperidone,

asenapine or paliperidone in BD depression, despite evidence of its efficacy in BD mania.

Combination treatment

Treatment with mood stabilizers is often insufficient in reducing depressive symptoms of BD, as opposed to their efficacy in reducing manic symptoms (Van Lieshout et al., 2010). Therefore, in clinical practice, antidepressants are commonly used as adjunctive therapy. However evidence for their efficacy is lacking and there are concerns with the potential to induce mania (Sidor and MacQueen 2011). There is some controversy on this topic; whereas it was typically assumed that antidepressants may induce a switch towards mania (especially when using tricyclic antidepressants) with evidence of higher switch rates in BD I compared with BD II (Bond et al., 2008), evidence from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study suggests that this risk is overrated (Perlis et al., 2010). The STEP-BD evaluates treatments for bipolar disorder with the aim to provide results that are generalizable to clinical practice. This study demonstrated that 21% of BD patients in a depressed phase switched towards mania but only 19% of that group were on antidepressants. In other words, switching to mania may not be specifically attributable to antidepressants rather there may generally be a risk of manic switch when depressive symptoms are attenuating, irrespective of treatment.

Table 4 summarizes the data from studies investigating combination treatment in BD depression. Three studies investigating adjunctive antidepressants (paroxetine, imipramine or agomelatine) did not demonstrate improvement of depressive symptoms in comparison to mood stabilizer monotherapy (Nemeroff et al., 2001; Sachs et al., 2007; Yatham et al., 2016). However it is important to note that while antidepressants were not beneficial, adding the antidepressant did not induce manic symptoms.

Adding the antipsychotic lurasidone to a mood stabilizer was more effective in reducing depressive symptoms compared with mood stabilizer monotherapy and was well tolerated (Loebel et al., 2014b). In contrast, adjunctive ziprasidone to a mood stabilizer was not beneficial in reducing depressive symptoms although it was well tolerated (Sachs et al., 2011b).

One combination of an antidepressant and an antipsychotic has been investigated in BD depression. Combining olanzapine and fluoxetine (OFC) has been demonstrated to be beneficial for BD depression compared with placebo with a low mania switch rate (Amsterdam et al., 2005; Tohen et al., 2003b;). OFC was more effective than lithium monotherapy (Brown et al., 2006) and olanzapine monotherapy (Tohen et al., 2003b). Although one study failed to show efficacy of OFC compared with lithium (Amsterdam et al., 2005) very few subjects were tested in each treatment group, perhaps influencing the power of the results.

Preliminary research on adjunctive modafinil and armodafinil suggested benefits in reducing depressive symptoms in BD compared with mood stabilizer monotherapy (Calabrese et al., 2010; Calabrese et al., 2014b; Frye et al., 2007). However these results could not be replicated in two other phase III trials (Frye et al., 2015; Ketter et al., 2015) and more research is necessary to determine its efficacy.

Discussion

While most second generation antipsychotics are effective in reducing manic symptoms, this is not the case for BD depression, with only a few drugs reducing depressive symptoms. Quetiapine, lurasidone, OFC, and the combination of lurasidone with lithium or valproate are the only FDA approved treatments of BD depression, while the EMA has only approved quetiapine (Wang et al., 2010). Evidence from the RCTS demonstrate their efficacy, however there is only RCT investigating lurasidone monotherapy and combination therapy, and more research is necessary relating to lurasidone.

Although lithium and valproate are effective as monotherapy for BD mania, there is limited data available to date in BD depression and current evidence suggests that lithium is less effective in treating the depressive phase of the illness, and more evidence (with larger sample sizes) in favor of valproate is needed. Evidence from RCTs of the efficacy of lamotrigine in reducing acute depressive symptoms is weak. However results from a meta-analysis (Geddes et al., 2009) demonstrated that lamotrigine improved the rate of response, which may explain why lamotrigine is widely used in clinical practice. In addition, benefits of lamotrigine were found to be related to the severity of depressive symptoms (Geddes et al., 2009), and this relationship warrants further investigations. Olanzapine was also effective as monotherapy in reducing depressive symptoms with the same metabolic side effects seen in mania.

Recently updated guidelines differ in their assessment and safety of antidepressants (Nivoli et al., 2011). Although some studies suggest a lower manic switch rate with SSRI compared with tricyclic and tetra cyclic antidepressants, the evidence for this is weak (Pacchiarotti et al., 2013). Guidelines commonly advise for caution in the use of antidepressants and give priority to mood stabilizers and antipsychotics. Specifically, to avoid the risk of a manic switch, antidepressants are advised only adjacent to mood stabilizing drugs (Pacchiarotti et al., 2013). This is in contrast to the prevalent use of antidepressants in clinical practice (Goodwin et al., 2008), which are in fact the most clinically employed treatment for BD depression (Baldessarini et al., 2008). While the role of antidepressants in treatment of BD depression continues to be controversial, evidence from RCTs suggests that they do not induce a manic switch, however there is also no evidence to suggest their efficacy.

Treatment of rapid cycling patients and patients with mixed features

Rapid cycling is a severe form of BD, and is often treatment resistant (Dunner et al., 1977) with poor response to lithium. It is therefore much more challenging to manage treatment in this subgroup of BD patients. Unfortunately, there are not many controlled studies conducted on treatment with rapid cycling patients. In a 20 month maintenance study (which included patients with BD I and BD II) comparing lithium and valproate in rapid cycling patients (Calabrese et al., 2005b), valproate was not superior to lithium monotherapy. One post-hoc analysis of olanzapine monotherapy in manic patients (Tohen et al., 1999), demonstrated that olanzapine was also effective in reducing manic symptoms in rapid cycling patients (Sanger et al., 2003), just as in non rapid cycling patients. One of the most challenging aspects of rapid cycling is the occurrence of frequent and severe episodes of depression. In one sub-analysis of a quetiapine monotherapy study (Calabrese et al., 2005a), it was found that quetiapine was also effective in reducing depressive symptoms for patients with a rapid cycling course of illness (Vieta et al., 2007). Lamotrigine may be useful in prolonging depressive episodes in rapid cycling patients (Calabrese et al., 2000). Combination treatment is standard in these patients, however there are no controlled trials investigating adjunctive therapy in this subgroup. There is controversy as to whether antidepressants can induce rapid cycling. Although there is no concrete evidence, to avoid any risk of antidepressants inducing and maintaining rapid cycling, antidepressants are advised only adjacent to mood stabilizing drugs (Pacchiarotti et al., 2013).

40% of patients with BD I experience mixed features (Fagiolini et al., 2013). These patients have poorer prognosis than those without (Angst et al., 2010; Fagiolini et al., 2013; Goldberg et al., 2009; Stahl et al., 2017) and are associated with rapid cycling, longer duration of illness, more lifetime episodes, more comorbidity and higher risk of suicide (Fagiolini et al., 2013; Stahl et al., 2017). Unfortunately, the majority of existing agents that have been evaluated in mixed patients have been

done using patients meeting DSM-IV criteria of a mixed state where both threshold level depression and mania are required. Very few studies have investigated pharmacotherapy using the more recently revised criteria of (subthreshold) mixed features in DSM-5. Thus, caution is advised when extrapolating evidence from bipolar disorder I without mixed features, as these have not been adequately investigated.

Two post hoc studies investigating olanzapine monotherapy also demonstrated efficacy in reducing manic and depressive symptoms in BD I patients with mixed features (Tohen et al., 2014a; Tohen et al., 2014b). Another post hoc study investigating lurasidone monotherapy also demonstrated efficacy in reducing manic and depressive symptoms in depressed BD I patients with mixed features (McIntyre et al., 2015). Safety and tolerability have not been assessed. Therefore, there are currently no FDA or EMA approved drugs for treatment of depression with mixed features, nor are there evidence based treatment guidelines. Nevertheless, it has been advised to firstly treat increased energy in mania with mixed features with valproate or an antipsychotic and to discontinue antidepressant use to avoid exacerbating manic symptoms (Fagiolini et al., 2013). Similarly, it has been advised in depression with mixed features to stop antidepressants if they may be exacerbating manic symptoms and to begin an antipsychotic or mood stabilizer. Adjunctive antidepressants should then be considered (Stahl et al., 2017).

Stabilization

Following treatment of acute episodes, maintaining a state of euthymia is the main goal in treating BD. This is critically important as it has been shown that each additional episode reduces quality of life (Mansell et al., 2005) and additionally has a negative impact on cognition (Bellivier et al., 2012), which also impacts functional outcome of the patients. Stabilization is achieved by long term medication use.

RCT trials investigating pharmacological treatment for over 6 months are few. In fact, the majority of treatments were not investigated and there are many

treatments with only one study to date. Table 5 summaries these studies. Studies have demonstrated that lithium effectively reduces the chance of relapse in BD patients compared with placebo (Bowden et al., 2000; Bowden et al., 2003; Calabrese et al, 2003; El Mallakh et al., 2012; Geddes et al., 2004). Valproate and carbamazepine were also found to be effective and comparable to lithium monotherapy (Bowden et al., 2000; Greil et al., 1997), however there were more negative side effects with carbamazepine making lithium a better option for maintenance. In addition, it was found that lithium treated BD patients had a decreased risk of suicide (Baldessarini et al., 2008). It is important to note that the course of the disorder may impact the success of treatment. It has been shown that BD I patients with a course of illness characterized by mania following episode of depression compared with mania preceding episodes of depression have worse response to long term lithium treatments (Koukopoulos et al., 2013). This is perhaps due to the fact that patients with a depressive-manic course usually present with more depressive episodes and more severe depressive episodes which are more difficult to treat.

Although lamotrigine has not been found to be effective in the acute stage of mania and there is not enough evidence for its efficacy in acute depression, studies have demonstrated that lamotrigine is effective as maintenance therapy compared with placebo (Bowden et al., 2003; Calabrese et al., 2003) and equally effective as lithium monotherapy in preventing relapse. In addition, lamotrigine was found to be effective in prolonging relapse for BD patients who had a rapid cycling course of illness (Calabrese et al., 2000). More specifically, lamotrigine was superior to lithium in preventing depressive episodes while lithium has been found to be better in preventing mania (Calabrese et al., 2003). Popovic (Popovic et al., 2012) suggests that predominant polarity is an important point to consider for pharmacotherapy and may guide the choice of maintenance treatment. Thus lamotrigine may be a good option for more depression prone patients.

Second generation antipsychotics have been investigated for maintenance both as monotherapy and in combination with lithium or valproate. Aripiprazole, risperidone ziprasidone and asenapine have been found to be effective for BD maintenance, both as monotherapy compared with placebo (Calabrese et al., 2017; El Mallakh et al., 2012; Keck et al., 2007; Quiroz et al., 2010; Szegedi et al., 2012) and as adjunctive therapy compared to mood stabilizer monotherapy (Bowden et al., 2010; Marcus et al., 2011; Macfadden et al., 2001). Aripiprazole was equally effective as lithium monotherapy (El Mallakh et al., 2012). Treatment with olanzapine (following successful stabilization of manic patients with olanzapine) was equally effective as valproate in reducing relapse rate (Tohen et al., 2003c) and more effective than lithium (Tohen et al., 2005; Tohen et al., 2006), but as in short term use of olanzapine, adverse events were common with olanzapine, specifically weight gain. Adding olanzapine to a mood stabilizer improved symptoms compared with monotherapy but did not improve relapse rate (Tohen et al., 2004). Quetiapine monotherapy was less effective in preventing relapse compared to lithium monotherapy (Berk et al., 2017), however adjunctive quetiapine (following stabilization with quetiapine) prolonged the time of relapse of both mania and depression compared with mood stabilizer monotherapy (Suppes et al., 2009; Vieta et al., 2008b), suggesting that adjunctive quetiapine is ideal.

It was found to be detrimental to continue with the antipsychotic perphenazine following remission (Zarate et al., 2004).

In a single study comparing OFC and lamotrigine (Brown et al., 2009), OFC was more effective in preventing relapse but had more side effects.

One RCT investigated the effects of long term treatment on cognitive functions by comparing quetiapine and lithium after a first episode of mania for 1 year (Daglas et al., 2016). They found that lithium but not quetiapine improved verbal fluency (which demands executive functioning). These results imply that protecting cognitive functions early in the course of the illness is also a priority as

cognitive decline is associated with poor functional outcome (Tabares-Seisdedos et al., 2008).

Discussion

Meta-analytic reviews of RCTs suggest that lithium and valproate are effective as first line maintenance treatment, as they prevent both manic and depressive relapse (see Connolly and Thase (2011) for review). Lithium is both FDA and EMA approved for maintenance treatment, however valproate is not FDA approved and EMA only consider valproate in patients who responded to it in a manic state (Wang et al., 2010). Although lamotrigine does not have strong evidence supporting its efficacy of acute treatment, it has demonstrated long term efficacy in preventing depressive relapse and it is FDA and EMA approved for maintenance. Aripiprazole, olanzapine, risperidone and ziprasidone demonstrated efficacy as maintenance against mania, however the only antipsychotic which showed efficacy against the recurrence of both manic and depressed symptoms is quetiapine plus lithium or valproate. These second generation antipsychotic treatments are FDA approved, however EMA has not approved the use of risperidone or ziprasidone for maintenance treatment in BD I (Wang et al., 2010).

As bipolar depression is so difficult to treat, clinicians often use a combination of treatments. Specifically, a second generation antipsychotic such as quetiapine or olanzapine which has rapid effects is used in combination with agents that have long term effects on depression such as lamotrigine. More research is necessary on these combinations. Connolly and Thase (2011) note that the majority of successful maintenance studies used a select population of subjects who were successfully treated during the acute stage of the illness, and continued treatment. As such, they advise maintenance therapy to be the medication to which they responded to acutely.

Importantly, specific psychiatric and medical comorbidities may largely influence the treatment choice. For example, an SSRI (for example OFC) is likely to be prescribed as treatment for patients with BD who present with comorbid anxiety disorder as SSRIs are also treatment for anxiety disorders. Antipsychotics should be avoided in individuals with BD who present with comorbid metabolic syndrome (or diabetes, hypercholestremia or obesitas), especially olanzapine, risperidone and quetiapine, which are known for its metabolic side effects.

Limitations

There are a number of limitations to this review. Firstly, many of the studies investigating lithium, valproate and carbamazepine were older studies compared with studies investigating newer agents. One of the many methodological differences between these studies is that placebo effects are known to be higher in more recent studies, which gives lithium an advantage. In addition, there are many methodological differences across studies. For example, different definitions of relapse are used, including the start of treatment, hospitalization or changes in rating scales. Many stabilization studies only used patients already stabilized with an experimental drug and might not reflect a true sample. These differences could differently influence results.

Another limitation is that the strength of the review lies in the available literature. For example, there are many studies demonstrating the efficacy of OFC and it has been approved for BD depression, olanzapine-fluoxetine is the only combination of an antipsychotic with an antidepressant that has been tested and other combinations may also be effective.

Very few long term longitudinal studies have been conducted, which is important for the assessment of the success of treatments. As mentioned above, the DSM criteria for BD I have shifted over the years, specifically the criteria for mixed features, which hampers the ability to generalize results from older studies.

Conclusion

Bipolar mania, a medical emergency has many treatment options which rapidly reduce the symptoms of mania, such as lithium, valproate and many second generation antipsychotics as monotherapy. When symptoms are severe and do not respond to monotherapy, combination of a second generation antipsychotic and lithium or valproate is recommended. Treatment for bipolar depression is still in question, with only quetiapine, lurasidone and OFC showing efficacy in reducing depressive symptoms and adjunctive lurasidone with lithium or valproate when symptoms are more severe. Treatment options in BD for maintenance of remission include lithium, valproate and adjunctive quetiapine which prevent both manic and depressive relapse. Lamotrigine is also approved for maintenance and is specifically useful in preventing depressive relapse.

Careful consideration of course of illness (including rapid cycling), predominant polarity and adverse effects of medication is essential before embarking on long term treatment. Although there are updated guidelines from the years 2014 and 2016 (Goodwin et al., 2016; Fountoulakis et al., 2016; Kendall et al., 2013), older guidelines need to be updated to meet shifting diagnostic criteria, for example relating to BD with mixed features. Research conducted on newer agents should also be assessed in future guidelines.

Expert Opinion

The key finding that has arisen from research on pharmacotherapy in BD I is the increased knowledge on treatment of acute mania. The ultimate goal of the research is to devise treatment plans across all stages of the illness. Unfortunately, treatment of bipolar depression and maintaining a state of euthymia remain a clinical challenge.

Depressive symptoms are the most enduring and disabling features of the disorder, even though mania is the distinguishing characteristic of BD I. These major depressive episodes may increase in frequency with increasing age and patients may become more resistant to antidepressant treatment, eventually dominating the clinical picture (Post et al., 2003). In addition and perhaps more importantly, residual depressive symptoms that persist between episodes in a third of the patients are a challenge because they impoverish strongly the quality of life of these patients. For this reason, it is critical to develop more research in finding treatment for the depressive phase of the illness. In addition, as major depressive disorder (MDD) and bipolar disorder both start off with depressive symptoms, the two disorders are extremely hard (or in the beginning, impossible) to distinguish. More research should focus on that issue and offer guidelines how to deal with MDD patients who do not respond to typical antidepressants and may in fact suffer from BD (with a manic episode still to reveal itself).

More efforts should also be made in investigating long term maintenance effects. As most studies focused on short term effects (up to the first 4 weeks), results from these studies do not take into account their long term tolerability, with drugs often presenting with late toxicities. Short term studies do not demonstrate the drug effects on both manic and depressive symptoms. More recently, research has focused on the relationship between drug efficacy and tolerability, which is critically important for drug compliance as drugs used in this context (mood stabilizers and antipsychotics) typically have important side effect profiles.

In addition to challenges directly related to the depression and maintenance stages of the illness, it is difficult for research to target the many different possibilities included in the complex nature of BD. It is known that cognitive deficits are present in patients with bipolar disorder and relate to poor functional outcome; nevertheless there is little research on the effects of pharmacotherapy of cognition in BD. It is important for treatment research to focus on cognitive deficits in order to aid clinicians in aiding their symptoms for better functioning

There are a number of limitations relating to the method of using RCT. Although randomised controlled trials are the best methodology for directly comparing different treatments amongst a comparable group of patients, RCTs do not represent 'real world' patients who present with all ranges of illness severity (including psychotic features or rapid cycling) and typically have a lot of comorbidity such as substance abuse and anxieties and additional cognitive deficits. It is therefore difficult for a clinician to extrapolate results from the RCTs. Thus the inclusion and exclusion criteria need to be looked at carefully in the design of studies and in interpreting the data. While observational studies may tell us more about BD, these studies are likely to be challenged for their validity. Ideally, a study should be open to 'all comers' in order to confidently assess the data, but because there are many subgroups to analyze, this will require very large studies. Secondly, although studies are officially controlled, in reality patients and doctors are often able to know whether they received the active treatment or placebo based on the side effects. This leads to an inherent bias.

It is important to note that many studies are driven by the pharmaceutical industry, with many negative studies not being published. This has great impact on practice and it is crucial to insist at study initiation an absolute right to publish results irrespective of outcome. Although several steps have been taken to install just that, we are still not seeing the publication of all performed studies (Goldacre 2014).

There is increasing need for new, more targeted treatments for BD I. Treatment for individuals with BD who have a 'less clean' profile needs to be investigated, as does treatment for patients with mixed features according to new criteria. More studies are also required in combination therapy, for example combining an antipsychotic and antidepressant other than OFC. New directions in the field should focus on minimising adverse long term effects, and long term studies are critical for this assessment. Although some new drugs have been tested in phase III (for example cariprazine), they did not demonstrate equal or superior effects to the golden standard drugs. We are in dire need of novel compounds with alternative

working mechanisms in order to further the field. It is expected that in the next few years new compounds will be investigated that have different working mechanisms (for example anti-inflammatory compounds such as P2X7 antagonists) that may play an important role in the future

Table 1: Overview of Randomized Controlled Trials on monotherapeutic treatment of mania in bipolar disorder

Study	Patien (N)	Patient type	Mear age	Sex (%Male)	Duration (week)	Comparators (dose)	Main outcome scales	Main findings
pope 1991	36	BDI Manic episode; DSM-III-R criteria for BD, manic episode	37.2	72	3	valproate (750 mg/d) placebo	YMRS	Valproate>placebo For manic symptoms
Small 1991	52	BD I manic or mixed, DSM-III-R criteria of BD	28.5	44	8	carbamazepine (from 200 mg/d) lithium (from 300 mg/d)	MRS, CGI	Carbamazepine= lithium for manic symptom
Freeman 1992	27	BD DSM-III criteria for manic episode	NA	33	3	valproate (1500-3000mg/d) lithium (up to 1800 mg/d)	SADS-C mania factor	Lithium = valproate for manic symptoms
Bowden 1994	179	BD I acutely manic; MRS>14	39.5	60	3	lithium (900-1200 mg/d) valproate (750-1000 mg/d) placebo	MRS	Valproate= lithium > placebo for manic symptoms

Segal 1998	45	BDI manic, DSM IV criteria	33.6	22	4	risperidone (6 mg/d) haloperidol (10 mg/d) lithium (800-1200mg/d)	MRS	Risperidone= haloperidol= lithium for manic symptoms, risperidone= haloperidol for extrapyramidal symptoms
Berk 1999	30	BDI manic episode, DSM-IV criteria	30.7	NA	4	olanzapine (10mg/d) lithium (400mg b.i.d)	MRS, CGI	Olanzapine= lithium for manic symptoms
Tohen 1999	139	BDI manic episode; YMRS>20	39.5	52	3	olanzapine (5-20 mg/d) placebo	YMRS, HDRS, CGI-BP	Olanzapine> placebo for manic symptoms, side effects= somnolence, dry mouth, dizzy and weight gain
Tohen 2000	115	BDI manic or mixed episode, 56% psychotic features; YMRS>20	38.5	29	4	olanzapine (5-20 mg/d) placebo	YMRS	Olanzapine> placebo for manic symptoms, more weight gain

Vasudev 2000	30	36 BDI manic episode, YMRS>20	NA	17	4	carbamazepine (800-1600 mg/d) valproate (1000-2200 mg/d)	YMRS	Carbamazepine= Valproate valproate was faster and better tolerated
Zajecka 2002	120	BDI acute mania; MRS>14	38.5	54	12	olanzapine (10-20 mg/d) valproate(20/mg/kg/d-1000mg/d +20/mg/kg/d)	MRS	Olanzapine= valproate for manic symptoms at 3 weeks. More weight gain with olanzapine
Keck 2003a	197	BDI manic or mixed (37%);MRS>14	38	54	3	ziprasidone (40-80 mg 2xd) placebo	SADS-C mania factor (MRS), CGI	Ziprasidone> placebo for manic symptoms by day 2; well tolerated
Keck 2003b	262	BDI manic or mixed (33%), 23% rapid cycling; YMRS>20	40.5	44	3	aripiprazole (30 mg/d) placebo	YMRS	Aripiprazole> placebo for manic symptoms by day 4; well tolerated

Tohen 2003a	453	BDI manic episode, 58% psychotic features; YMRS>20	40	40	12	olanzapine (5-20 mg/d) haloperidol (3-15 mg/d)	YMRS	Haloperidol= Olanzapine for manic symptoms; haloperidol: faster switch depression, worse extrapyramidal symptoms. Olanzapine: weight Gain
Hirschfeld 2004	259	BDI manic episode, 43% psychotic features; YMRS>20	38.8	57	3	risperidone (1-6 mg/d) placebo	YMRS, CGI	Risperidone> Placebo from 3 days for manic symptoms
Weisler 2004	204	BD I manic or mixed (53%); YMRS>20	38	53	3	carbamazepine extended release capsule placebo	YMRS, CGI	Carbamazepine> placebo for manic symptom
Bowden 2005	300	BD I manic episode, 28% psychotic features; YMRS>20	39.3	58	12	quetiapine (up to 800 mg/d) lithium (starting at 900 mg/d) placebo	YMRS, CGI-BP	Quetiapine= lithium> placebo for manic symptoms. Genreally well Tolerated

Khanna 2005	290	BDI manic or mixed (5%) , 59% psychotic features; YMRS>20	35.1	62	3	risperidone (1-6 mg/d) placebo	YMRS	Risperidone> placebo for manic symptoms from week 1; well tolerated
McIntyre 2005	151	BDI manic episode; YMRS>20	42.8	37	12	quetiapine (400-800 mg/d) haloperidol (up to 8 mg/d) placebo	YMRS, CGI-BP	Quetiapine= Haloperidol for manic symptoms (3 and 12 weeks); more motor symptoms with haloperidol
Potkin 2005	202	BDI manic episode;MRS> 14	38.9	52	3	ziprasidone (40-80 mg/d) placebo	SADS-CB (MRS), CGI	Ziprasidone>placebo for manic symptoms from day 2, well tolerated
Smulevich 2005	227	BD I manic episode, 33% psychotic features; YMRS >20	39.7	77	12	risperidone (1-6 mg/d) haloperidol (2-12 mg/d) placebo	YMRS, CGI, MADRS	Risperidone=haloperidol>placebo for manic symptoms. less adverse events with risperidone
Vieta 2005	347	BDI manic or mixed episode (11%); YMRS>20	41.8	38	12	aripiprazole (15-30 mg/d) haloperidol (10-15 mg/d)	YMRS	Aripiprazole>haloperidol for manic symptoms; more extrapyramidal symptoms with haloperidol

Weisler 2005	239	BDI manic or mixed (21%) episode; YMRS>20	37	70	3	carbamazepine extended release (200-1600 mg/d) placebo	YMRS, CGI	Carbamazepine> placebo for manic symptoms, side effects include dizzy, somnolence, nausea
Bowden 2006	377	BD I manic, 88% mixed, 21% with psychotic features; MRS>14	37.6	57	3	valproate placebo	MRS	Valproate > placebo for manic symptoms
Kushner 2006	439	BD I manic or mixed type; YMRS>20; 4 trials	42.5	48	12	topirmate (200 mg/d) topiramate (400 mg/d) topiramate (600 mg/d) lithium (1500 mg/d) placebo	YMRS	Lithium > Topiramate= placebo for manic symptoms; topiramate side effects: appetite decrease, paresthesia, dry mouth and weight loss.
Perlis 2006	329	BDI manic or mixed (58%), no psychotic features; YMRS>20	37.9	45	3	olanzapine (5-20 mg/d) risperidone (1-6 mg/d)	YMRS	Olanzapine=risperidone for manic symptoms

Sachs 2006	272	BDI manic or mixed episode; YMRS>20	38.8	49	3	aripiprazole (30 mg/d) placebo	YMRS	Aripiprazole>placebo for manic symptoms from day 4 and well tolerated
Niufan 2008	140	BDI manic episode, 14% psychotic features; YMRS>20	32.6	47	4	olanzapine (5-20 mg/d) lithium (600-1800 mg/d)	CGI-BP, YMRS	Olanzapine>Lithium for manic symptoms but more side effects, weight gain
Tohen 2008	306	BDI manic episode; YMRS>20	39.8	49	12	olanzapine (5-20 mg/d) valproate (500-2500 mg/d) placebo	YMRS	Olanzapine= valproate>placebo at 3 weeks , olanzapine>valproate at 12 weeks; more adverse side effects
Yildiz 2008	66	BDI manic episode, YMRS>20	32.5	49	3	tamoxifen (40-80 mg/d) placebo	YMRS	Tamoxifen reduced YMRS scores and was well tolerated
Keck 2009	480	BDI manic or mixed (39%), 23%psychotic features; YMRS>20	39.7	83	12	aripiprazole (15-30 mg/d) lithium (900-1500 mg/d) placebo	YMRS	Aripiprazole =lithium> placebo for manic symptoms at 12 weeks. Aripiprazole was faster, from day 2. Relatively well tolerated

Kakkar 2009	60	60 BDI acute mania; YMRS>20	29	55	12	oxcarbazpine (1000-2400 mg/d) valproate (750-2000 mg/d)	YMRS	Oxcarbamazepine= valproate for manic symptom, less side effects
McIntyre 2009	489	BDI manic or mixed episode(31%); YMRS>20	39.4	57	3	asenapine (10 mg/d) olanzapine (5-20 mg/d) placebo	YMRS	Asenapine> placebo for manic symptoms (as early as day 2); well tolerated
Young 2009	274	BDI manic or mixed, with or without psychotic features; YMRS>20	40.8	44	12	aripiprazole (30 mg/d) haloperidol (5-15 mg/d) placebo	YMRS	Aripiprazole=Haloperidol >Placebo for manic symptoms (3 and 12 weeks). Aripiprazole was better tolerated
El Mallakh 2010	401	BDI manic or mixed (39%), 20% rapid cycling; YMRS>20	40.4	48	3	aripiprazole (15 mg/d) aripiprazole (30 mg/d) placebo	YMRS	Aripiprazole=placebo for manic symptoms
Hirschfeld 2010	225	BDI manic or mixed type, YMRS>20	39.5	50	3	valproate extended release (500-2500 mg/d) placebo	MRS	Valproate= placebo for manic symptoms

McIntyre 2010	488	BDI manic or mixed episode (31%); YMRS>20	38.6	52	3	asenapine (5-10 mg/d) olanzapine (5-20 mg/d) placebo	YMRS	Asenapine>placebo for manic symptoms as early as day 2
Shafti 2010	40	BDI manic episode, all female	NA	NA	3	lithium (300 mg/d) olanzapine(5 mg/d)	MRS, CGI	Olanzapine=lithium for manic symptoms, more weight gain with olanzapine
Vieta 2010a	176	BDI I manic episode; MRS>14	38.1	59	12	ziprasidone (40- 160 mg/d) haloperidol (4-30 mg/d) placebo	MRS	Ziprasidone=haloperidol, but haloperidol caused more movement disorders
Vieta 2010b	388	BDI manic or mixed episode (36%) ; YMRS>20	39	57	12	paliperidone (3-12 mg/d) quetiapine (400-800 mg/d) placebo	YMRS, CGI-BP	Paliperidone=quetiapine> placebo for manic symptoms (3 and 12 weeks)
Cutler 2011	308	BDI manic or mixed, with or without rapid cycling; YMRS>20	41	61	3	quetiapine extended release (400-800 mg/d) placebo	YMRS, CGI-BP	Quetiapine extended release>placebo for manic symptoms from day 4

Li 2008	155	BDI manic episode, all Chinese, 28%psychotic features; YMRS>20	33.2	47	4	quetiapine (200-800 mg/d) lithium (500-2000mg/d)	YMRS, MADRS	Quetiapine =lithium for manic symptoms
Berwaerts 2012	449	BDI manic episode, 37% mixed 23% psychotic features; YMR>20	39.5	54	3	paliperidone (3 mg/d) paliperidone (6mg/d) Paliperidone (12mg/d) placebo	YMRS	Paliperidone 12 mg/d > placebo for manic symptoms
Kanba 2012	258	BD I manic or mixed (11%), 36% psychotic features; YMRS >20	37.7	41	3	aripiprazole (12-24 mg/d) placebo	YMRS	Aripiprazole > placebo for mania, generally well tolerated
Katagiri 2012	224	BD I manic or mixed (7%), 18%psychotic features; YMRS >20	44.9	48	6	olanzapine (5-20 mg/d) haloperidol (2.5-10 mg/d) placebo	YMRS, CGI-BP	Olanzapine=Haloperidol> placebo; fewer switched to depression with olanzapine. Small haloperidol sample.

Calabrese 2014a	497	BD I manic or mixed, with or without psychotic features; YMRS>20	41.9	53	3	cariprazine (3-6mg/d) Cariprazine (6-12mg/d) placebo	YMRS, CGI-S	Cariprazine (both doses) > placebo for mania symptoms and well tolerated. Higher dose=more acathisia
Sachs 2015	312	BDI manic or mixed episode; YMRS>20	36.2	65	3	cariprazine (3-12 mg/d) placebo	YMRS, CGI-S	Cariprazine>placebo for manic symptoms and generally well tolerated
Landbloom 2016	367	BDI manic or mixed episode (29%);YMRS>20	43.8	45	3	asenapine (5 mg/d) asenapine (10 mg/d) placebo	YMRS, CGI-BP	Asenapine (both doses) > placebo for manic symptoms, well tolerated

Abbreviations: BD=bipolar disorder; NA=not available; MRS=Mania Rating Scale; CGI=Clinical Global Impression; CGI-BP=Clinical Global Impression-bipolar version; CGI-S=Clinical Global Impression-severity; YMRS=Young Mania Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; HDRS/HAMD= Hamilton Depression Rating Scale; SADS=Schedule for Affective Disorders and Schizophrenia

Table 3: Overview of Randomized Controlled Trials on combination treatment of mania in bipolar disorder

Study	Patients (N)	Patient type	Mean age	Sex (% male)	Duration (week)	Comparator A (dose)	Comparator B (dose)	Main outcome scales	Main findings
Garfinkel 1980	21	BD I manic episode	38.5	47	3	lithium (900 mg/d) + haloperidol (30 mg/d)	haloperidol + placebo/ lithium + placebo	BPRS, EPS Neurological rating scale	Haloperidol + placebo= haloperidol+ lithium > lithium+placebo for manic symptoms.
Chou 1999	63	BD I manic episode with psychotic features	34.5	63	3	haloperidol (5 mg/d) + lithium/ lorazepam/ placebo	haloperidol (25 mg/d) + lithium/ lorazepam/ placebo	Manic State Rating Scale	High dose haloperidol had most improvement, but more side effects. Low dose haloperidol too low. Low dose + lithium enhanced effect of haloperidol response. Adjunctive lorazepam did not add anything.
Pande 2000	117	BD I manic or mixed (23%) episode; YMRS > 12	39.5	52	10	gabapentin (900-3600 mg/d) + lithium/valproate	lithium/valproate +placebo	YMRS	Adjunctive gabapentin < placebo for manic symptoms

Sachs 2002	156	BD I manic or mixed (21%) episode; YMRS>20	43	51	3	risperidone (2-6 mg/d) + mood stabilizer / haloperidol (4-12 mg/d) + mood	mood stabilizer +placebo	YMRS, BPRS, CGI	Risperidone or haloperidol + mood stabilizer> mood stabilizer for rapid control of manic symptoms and well tolerated
Tohen 2002	344	BD I manic , 51%mixed ; YMRS>16	40.5	50	6	olanzapine (5-20 mg/d) + lithium/valproate	lithium/valproate +placebo	YMRS	Adjunctive olanzapine >lithium monotherapy, more side effects with olanzapine: weight gain, tremor, slurred speech
Weisler 2003	205	BD I manic or mixed episode; MRS>14	18	NA	3	ziprasidone (80-160 mg/d)+ lithium	lithium+ placebo	MRS, CGI-S	Combination > lithium for manic symptoms at day 4, =at 2-3 weeks.
Yatham 2003	151	BD I manic episode 8% mixed , 43% psychotic features; YMRS>20	39.5	42	3	risperidone (2-6 mg/d) + mood stabilizer	mood stabilizer +placebo	YMRS	Adjunctive risperidone> mood monotherapy from week 1

Sachs 2004	191	BD I manic episode; 25% psychotic features; YMRS>20	40.5	56	3	quetiapine (up to 800 mg/d) + lithium/ valproate	lithium/valproate +placebo	YMRS,CGI-BP	Adjunctive quetiapine > mood stabilizer monotherapy for manic symptoms, well tolerated
chengappa 2006	287	BDI manic or mixed episode (23%), 28% rapid cycling, 27% psychotic features; YMRS>18	40	43	12	topiramate (25-400 mg/d) + Lithium/valproate	lithium/valproate +placebo	YMRS	Adjunctive topiramate=mood stabilizer monotherapy for manic symptoms, significant weight loss
Yatham 2007	200	BDI manic episode, 43%psychotic features; YMRS>20	39.5	50	6	quetiapine (up to 800 mg/d) + lithium/valproate	lithium/valproate +placebo	YMRS	No difference in YMRS reduction between the groups.
Machado-Vieira 2008	180	BD I manic episode; YMRS>22	28.5	43	4	allopurinbol (600 mg/d) +lithium	lithium + placebo dipyridamole (200mg/d) +lithium	YMRS	Adjunctive allopurinol>dipyridamole for manic symptoms

Tohen 2008b	118	BD I manic or mixed episode; YMRS >20	40.7	42	6	olanzapine (10-30 mg/d) + carbamazepine	carbamazepine+ placebo	YMRS, MADRS, CGI-BP	Olanzapine+carbamazepine= carbamazepine and more weight gain
Vieta 2008a	384	BDI manic or mixed 26% episode; YMRS>16	41.9	45	6	aripiprazole (15-30 mg/d) + lithium or valproate	lithium/valproate +placebo	YMRS, CGI-BP	Adjunctive aripiprazole > lithium or valproate from week 1, well tolerated
Amrollahi 2011	40	BD I manic episode	61.4	60	6	tamoxifen (80 mg/d) +lithium	lithium + placebo	YMRS	Adjunctive tamoxifen> lithium monotherapy for manic symptoms, well tolerated
Berwaerts 2011	300	BD I manic or mixed episode; YMRS >20	40	54	6	paliperidone extended release (3-12 mg/d)+ mood stabilizer	mood stabilizer +placebo	YMRS	Adjunctive paliperidone=mood stabilizer monotherapy for manic symptoms, more adverse events, insomnia
Sachs 2012	680	BD I manic or mixed (38%) episode; YMRS>18	41.4	58	3	ziprasidone (20-40 mg/2xd) ziprasidone (60-80 mg/2xd) + lithium/valproate	lithium/valproate +placebo	YMRS,MADRS, CGI	Adjunctive ziprasidone = mood stabilizer monotherapy

Szegedi 2012	324	BDI manic episode, 33% mixed; YMRS>20	39.3	58	12 (core study)	asenapine (5-10 mg/d) + lithium/valproate	lithium/valproate +placebo	YMRS, CGI-BP	Adjunctive asenapine> lithium/valproate for BD mania
Bourin 2014	356	BD I manic or mixed episode (7%); YMRS >20	38.3	62	6	quetiapine extended release (400-800 mg/d) + lithium (600-1800 mg/d)	quetiapine+ placebo	YMRS	Adjunctive quetiapine> quetiapine monotherapy, well tolerated
Jahangard 2014	50	BDI manic episode; YMRS>28	34.4	61	4	valproate(5-20mg/Kg) + allopurinol (300 mg 2x/d)	valpraote + placebo	YMRS, CGI	Allopurinol+valproate > valproate for manic symptoms
Moosavi 2014	48	BD I manic phase no psychotic features	25	59	7	risperidone (6-8 mg/d) + valproate (800-1200 mg/d)	risperidone (6-8 mg/d) +placebo	remission based on DSM IV TR	risperidone+valproate = risperidone monotherapy for remission rate, adverse events
Weiser 2014	180	BD I manic episode	46.7	33	6	allopurinol (300 mg/d)+ any previous treatment (mood and/or antipsychotic)	previous treatment+ placebo	YMRS	Adjunctive allopurinol=placebo for manic symptoms

Xu 2015	120	BD I manic episode, 25% mixed; YMRS>17	30.9	48	4	olanzapine (10mg/d) + valproate (600 mg/d)	valproate (600mg/d) olanzapine (10mg/D)	YMRS, CGI-BP	Combination therapy> monotherapy in BD mania

Abbreviations: BD=bipolar disorder; NA=not available; MRS=Mania Rating Scale; CGI=Clinical Global Impression; CGI-BP=Clinical Global Impression-bipolar version; CGI-S=Clinical Global Impression-severity; YMRS=Young Mania Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; BPRS=Brief Psychiatric Rating Scale; EPS= Extrapyramidal side effects

Table 3: Overview of Randomized Controlled Trials on monotherapeutic treatment of depression in bipolar disorder

Study	Patients (N)	Patient type	Mean age	Sex (% male)	Duration (weeks)	Comparators (dose)	Main outcome scales	Main findings
Calabrese 1999	195	BD I depression; HAMD >18	41.6	39	7	lamotrigine (50 mg/d) lamotrigine (200 mg/d) placebo	HAMD,MADRS, MRS, CGI	Lamotrigine (both doses)> placebo for BD depression as early as 3 weeks, well tolerated.
Tohen 2003b	456	BD I depression; MADRS>20	41.8	37	8	olanzapine (5-20 mg/d) olanzapine/fluoxetine (6 and 25, 6 and 50, 12 and 50mg/d) placebo	MADRS	OFC> olanzapine > placebo for depressive symptom without increased risk of manic symptoms
Calabrese 2005a	360	BD I depressive episode (182 BDII analyzed separately)	37.4	42	8	quetiapine (600 mg/d) quetiapine (300 mg/d) placebo	MADRS	Quetiapine (both doses) > placebo for depressive symptoms. Manic episodes were low
Davis 2005	25	BD I depressed episode; HDRS >16	41	89	8	valproate (2500 mg/d) placebo	HDRS, CGI	Valproate>placebo for depression. Small sample

Thase 2006	509	BD depressive episode; BD I in majority of patients (analyzed separately)	37.7	43	8	quetiapine (300 mg/d) quetiapine (600 mg/d) placebo	MADRS	Quetiapine (both doses)>placebo for depression
Calabrese 2008 Trial 1: Trial 3: Trial 5:	 195 257 259	BD I depressive episode; HAMD>18	 42.3 37.5 39.4	 43 45 46	 7 8 8	lamotrigine (200mg/d) placebo	Trial 1: HAMD; CGI-I Trial 3,5:MADRS; CGI-I	In all trials, lamotrigine=placebo for BD depression. No active switch to mania, relatively well tolerated
Thase 2008 Trial 1: Tiral 2:	 374 375	BD I depression	 39 40.5	 37 40	8	Trial 1: aripiprazole(5-30 mg/d) placebo Trial 2: aripiprazole (5-30 mg/d) placebo	MADRS; CGI-BP	Aripiprazole=placebo for depression at 8 weeks, Improvement at week 5-6

McElroy et al., 2010	448	BD I depressive episode; HDRS>20 (Patients with BDII were investigated separately)	38.7	37	8	quetiapine (300 mg/d) quetiapine (600 mg/d) paroxetine (20 mg/d) placebo	MADRS; CGI-BP-S	Quetiapine (not paroxetine)>placebo for depressive symptoms, generally well tolerated
Young 2010	487	BD I depressive episode (majority of patients) (296 BD II analyzed separately); HDRS>20)	42.2	41	8	quetiapine (300 mg/d) quetiapine (600 mg/d) lithium (600-1800 mg/d) placebo	MADRS, HDRS	Quetiapine (both doses)> placebo and lithium on depressive symptoms.
Muzina 2011	54	BD depressed episode; 20 BD1 34 BDII	39.2	43	6	valproate placebo	MADRS	Valproate > placebo for BD depression in BD I and BD II

Lombardo 2012 Trial 1: Trial 2:	 171 133	BDI depression; HAMD >20	N/A	N/A	Both trials : 6	Trial 1: ziprasidone (40-80 mg/d) ziprasidone (120-160 mg/d) placebo Trial 2: ziprasidone (40-160 mg/d) placebo	MADRS; CGI-I	In both trials, ziprasidone= placebo for depressive symptoms
Tohen 2012	514	BD I depression; HDRS>18	35.5	58	6	olanzapine (5-20 mg/d) placebo	MADRS; CGI-BP	Olanzapine>placebo for depressive symptoms, more weight gain
Loebel 2014a	335	BD I depressive episode , no psychotic features; MADRS>20	41.5	43	6	lurasidone(20-60 mg/d) lurasidone (80-120 mg/d) placebo	MADRS, CGI-BP	Lurasidone (both doses)>placebo for depression.
Suppes 2014	217	BD depressive episode; HDRS>20. A few BD II were separately analyzed	39.5	36	8	quetiapine extended release (300 mg/d) placebo	MADRS	Quetiapine extended release > placebo for depression as early as day 7. Dry mouth, somnolence,sedation and weight gain

Wang 2014	64	BD I depression, MADRS>20	29.2	41	8	olanzapine (mean 10-20 mg/d) placebo	MADRS; CGI	Olanzapine >placebo for depression but metabolic side effects

Abbreviations: BD=bipolar disorder; NA=not available; MRS=Mania Rating Scale; CGI=Clinical Global Impression; CGI-BP=Clinical Global Impression-bipolar version; CGI-S=Clinical Global Impression-severity; CGI-I=Clinical Global Impression-global improvement; MADRS=Montgomery-Asberg Depression Rating Scale; HDRS/HAMD= Hamilton Depression Rating Scale

Table 4: Overview of Randomized Controlled Trials on combination treatment of depression in bipolar disorder

Study	Patients (N)	Patient type	Mean age	Sex (% male)	Duration (weeks)	Comparator A (dose)	Comparator B (dose)	Main outcome scales	Main findings
Nemeroff 2001	117	BD I depressive episode	42.5	NA	10	paroxetine + lithium/valproate/ carbamazepine Imipramine + lithium/valproate/ carbamazepine	lithium/ valproate/ carbamazepine + placebo	HAMD, CGI	All treatments =placebo. Both> for patients with low serum lithium levels. Paroxetine had less adverse events for mania.
Tohen 2003	833	BD I depressive episode; MADRS> 20	41.8	37	8	olanzapine + fluoxetine (6 and 25, 6 and 50, 12 and 50mg/d)	olanzapine (5-20 mg/d) + placebo	MADRS	OFC > olanzapine for depressive symptoms without increased risk of manic symptoms
Amsterdam 2005	32	BD I (+ 2 BD II) depressive episode; HDRS>18	40	76	8	fluoxetine (10-30 mg/d) olanzapine (5-20 mg/d) combination fluoxetine (10-40 mg/d) +olanzapine (5-15 mg/d)	placebo	HAMD; MADRS, YMRS	Olanzapine=fluoxetine =OFC > placebo for depressive symptoms. No increase in mania.

Brown 2006	410	BD I depressive episode	37	40	7	olanzapine + fluoxetine (6 and 25, 6 and 50, 12 and 25, 12 and 50mg/d)	lamotrigine (200mg/d)	CGI-S	OFC > lamotrigine for depressive symptoms, more weight gain
Frye 2007	64	BD I (21 BD II) depressive episode; IDS >16	42.4	43	6	modafinil (100-200 mg/d) + mood stabilizer	mood stabilizer +placebo	IDS, CGI-BP, YMRS	Modafinil > placebo for depressive symptoms, even better in BD I. This low dose did not affect attention, well tolerated
Sachs 2007	354	BD depressive episode (114 BD II)	40	43	26	paroxetine (10-40 mg/d) +mood stabilizer bupropion (150-375 mg/d) + mood stabilizer	mood stabilizer +placebo	SUM-D	Adjunctive antidepressants=placebo, no treatment emergent mania.
Calabrese 2010	257	BD I depressive episode; QIDS ≥13, CGI-S ≥4,	43.8	46	8	armodafinil (150 mg/d) + lithium, valproate or olanzapine	lithium, valproate or olanzapine + placebo	IDS	Adjunctive armodafinil > placebo for depressive symptoms, well tolerated.
Sachs 2011	298	BD I depressive episode; HDRS >20	40.4	57	6	ziprasidone (20-80 mg/2xd) +mood stabilizer	mood stabilizer +placebo	MADRS, CGI-S	Adjunctive ziprasidone = mood stabilizer alone, well tolerated

Calabrese 2014b	433	BD I depression, IDS >13	44	30	8	armodafinil (150 mg/d) + mood stabilizer armodafinil (200mg/d) + mood stabilizer Placebo	Placebo + mood stabilizer	IDS	Adjunctive armodafinil >placebo for depressive symptoms ,no induction of mania, generally well tolerated
Loebel 2014b	348	BD I depression, MADRS score >20	41.8	53	6	lurasidone (20-120 mg/d)+lithium/valproate	lithium/valproate + placebo	MADRS, CGI-BP	Adjunctive lurasidone > placebo for depressive symptoms, well tolerated
Frye 2015	399	BD I depressive episode; QIDS ≥13, CGI-S ≥4	44.5	40	8	Armodafinil (150 mg/d) + maintenance treatment	maintenance treatment + placebo	IDS	Adjunctive armodafinil = placebo for depressive symptoms, well tolerated.
Ketter 2015	490	BD I depression, >13 IDS score	43.1	41	8	armodafinil (150 mg/d) + maintenance treatment Armodafinil (200 mg/d) + maintenance treatment	Pplacebo + additional maintenance treatment	IDS	Armodafinil = placebo for depressive symptoms, well tolerated.

Yatham 2016	344	BD I depressive episode; HDRS>18	45.2	59	8 or 52	agomelatine (25-50 mg/d) + lithium/valproate	lithium/valproate + placebo	MADRS		Adjunctive agomelatine=placebo for depression, it was not associated with high level of mania

Abbreviations: BD=bipolar disorder; NA=not available; CGI=Clinical Global Impression; CGI-BP=Clinical Global Impression-bipolar version; CGI-S=Clinical Global Impression-severity; MADRS=Montgomery-Asberg Depression Rating Scale; HDRS/HAMD= Hamilton Depression Rating Scale; IDS= Inventory for Depressive Symptoms; QIDS=Quick Inventory for Depressive Symptoms; SUM-D = Depression subscale of Clinical Monitoring Form

Table 5: Overview of Randomized Controlled Trials on maintenance treatment in bipolar disorder

Study	Patients (N)	Patient group	Mean age	Sex (%male)	Duration (weeks)	Comparators	Relapse criteria	Main outcome
Greil 1997	144	BD I	44	48	130	Following stabilization: lithium carbamazepine (4-12 µg/ml)	Research diagnostic criteria score of 5	No difference in hospitalizations , lithium<side effects
Bowden 2000	372	BD I, MRS=3.4	39	49	52	Following stabilization: valproate lithium placebo	Occurrence of a manic episode (MRS score >16 or hospitalization), or depressive episode	Valproate=lithium for relapse rate
Calabrese 2000	182	BD I , manic or depressed rapid cycling	38	43	26	Following stabilization: lamotrigine (100-500 mg/d) placebo	Requiring intervention	Lamotrigine >placebo for relapse rate, well tolerated
Bowden 2003	175	BD I manic episode	41	47	76	Following stabilization: lamotrigine lithium placebo	Requiring intervention	Lamotrigine= lithium>placebo relapse; lamotrigine very good for preventing depression.

Calabrese 2003	463	BD I depressed episode	44	44	76	lamotrigine (50, 200 or 400 mg/d) lithium placebo	requiring intervention	Lamotrigine= lithium >placebo in preventing relapse. Lamotrigine> preventing depression, lithium >for mania.
Tohen 2003	251	BD I manic episode	41	43	47	olanzapine (5-20 mg/d) Valproate (500-2500 mg/d)	YMRS or HAMD >15	Olanzapine=valproate for rate to relapse. Olanzapine had more side effects
Tohen 2004	99	BD I stabilized from manic episode	41	48	78	Following stabilization: olanzapine (5-20 mg/d) +lithium/valproate placebo+ lithium/valproate	Symptomatic according to YMRS or HAMD	Adjunctive olanzapine=mood stabilizer in preventing relapse of mania or depression (DSM criteria) but some symptoms were prevented with combination.
Zarate 2004	37	BD I manic episode	36	24	26	perphenazine (4-64 mg/d) +mood placebo+mood	DSM-IV criteria for a manic or depressive episode	Detrimental to continue with this typical antipsychotic following remission

Tohen 2005	431	BD I manic episode	42	47	52	Following stabilization: olanzapine (5-20 mg/d) lithium	YMRS or HAMD>15	Olanzapine> lithium in preventing manic episode but equal in preventing depression, more weight gain
Tohen 2006	361	BD I 66% manic	40	39	48	Following stabilization: olanzapine (5-20 mg/d) placebo	YMRS or HAMD>15 or hospitalization	Olanzapine delayed relapse in manic patients who responded to olanzapine, additional weight gain
Keck 2007	161	BD I 70% manic	40	33	100	Following stabilization: Aripiprazole (15-30 mg/d) placebo	Hospital admission or increased medication	Aripiprazole>placebo for relapse of manic episode in patients who were initially stabilized on aripiprazole for 6 consecutive weeks, good tolerability

Vieta 2008b	703	BD I 48% manic	42	45	104	Following stabilization: quetiapine (400-800 mg/d) + lithium/valproate placebo+li/val	YMRS or MADRS>20 or hospitalization	Adjunctive quetiapine>mood stabilizer in preventing relapse of both manic and depressive episodes
Brown 2009	410	BD I depressive episode MADRS>20	37	40	25	Olanzapine (6 or 12 mg/d) + Fluoxetine (25 or 50 mg/d) Lamotrigine (150-200 mg/d)	MADRS, CGI-S	OFC>lamotrigine for depressive symptoms but more adverse events, weight gain and higher cholesterol
MacFadden 2009	124	BD frequently relapsing	39	72	52	following stabilization: Risperidone long acting injectable (25-50 mg/d) +mood stabilizer Mood stabilizer	YMRS>15 or hospitalization	Adjunctive risperidone> mood stabilizer for rate of relapse. Well tolerated

Suppes 2009	623	BD I 24% manic	40	48	104	Following stabilization: quetiapine (400-800 mg/d) + mood stabilizer placebo+mood stabilizer	Requiring more treatment, hospitalization, YMRS>20	Adjunctive quetiapine reduced time to relapse
Bowden 2010	240	BD I manic episode MRS>14	38.8	47	26	mood+ ziprasidone (80-160 mg/d) mood +placebo	Time until next mood episode	Adjunctive ziprasidone> monotherapy for relapse rate, well tolerated
Quiroz 2010	303	BD I 79% manic	39	51	104	Following stabilization: Risperidone long-acting injectable (12.5-50 mg/d) placebo	YMRS>12 or needing more risperidone	Risperidone long acting injectable>placebo in reducing mood episode, well tolerated
Marcus 2011	337	BD I manic episode , 32% mixed YMRS>16	39	45	52	aripiprazole (10-30 mg/d)+ lithium/valproate placebo+lithium or valproate	YMRS	Adjunctive aripiprazole >mood stabilizer for time to relapse, well tolerated.

El Mallakh 2012	99	Manic episode (YMRS>20)	39.2	45	52	Lithium Aripiprazole placebo	YMRS	Aripiprazole = lithium>placebo for long term treatment of mania
Szegedi 2012	77	BD I manic episode;, 33% mixed; YMRS>20	39.3	58	52	asenapine (5-10 mg/d) +lithium/valpraote placebo + lithium/ valproate	YMRS, CGI-BP	Adjunctive asenapine> lithium/valproate for mania and was well tolerated
Berk 2017	61	BD I manic episode first episode, YMRS >20	21	78	52	Following stabilization with quetiapine+mood: quetiapine (up to 800 mg/d) lithium	Hospitalization, psychosis, depressive or manic relapse (YMRS, MADRS)	lithium> quetiapine
Calabrese 2017	266	BD I manic episode, YMRS >20	40.6	43	52	Following stabilization with aripiprazole: aripiprazole once monthly 400 mg placebo	Recurrence of mood episode	Aripiprazole >placebo for relapse

Abbreviations: BD=bipolar disorder; CGI-BP; MRS=Mania Rating Scale; CGI-BP=Clinical Global Impression-bipolar version
YMRS=Young Mania Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; HDRS/HAMD= Hamilton Depression Rating Scale

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Chapter 7

General discussion

Cognitive and psychomotor abnormalities are prominent clinical features of bipolar disorder (BD). These are particularly important areas of research because they are symptoms of the illness that require more attention in treatment. Thus, when individuals with BD achieve affective remission, they nevertheless continue to experience cognitive and psychomotor difficulties which contribute directly to difficulties in everyday functioning. Importantly, many cognitive difficulties present in BD may be directly involved in psychomotor functioning. The research in this thesis focuses on an in-depth investigation of underlying mechanisms and cognitive sub-processes relating to psychomotor abnormalities in euthymic BD, where research has been lacking. This is critically important as identifying underlying abnormalities present in BD may be useful treatment targets, and may improve overall functioning in BD.

First, a summary of the research aims and how the research was carried out together with relevant results are presented. This is followed by the implications of the results for understanding the pathogenesis of BD and the neural circuitries implicated in psychomotor functioning difficulties in BD. The findings presented in the thesis are then discussed in light of previous research in schizophrenia and major depressive disorder (MDD), two related disorders. The implications for treatment are then described. Limitations of the current studies and suggestions for future research are considered and followed by an overall summary of the findings.

Summary of research aims and relevant results

Cognitive deficits are critical features of BD, persisting in euthymia and interfere with the overall functioning of the individuals (Sole et al., 2017). These include deficits in attention, verbal memory, executive functions and psychomotor speed (Bourne et al., 2013). Disturbances in psychomotor speed are observable and measureable behaviors in BD. However, movements involve numerous underlying cognitive processes ranging from motor selection, planning, preparation, motor

programming, initiation, task switching, response inhibition, error detection and performance monitoring, whereby dysfunction at any stage can result in disturbed psychomotor functioning. In other words, in addition to muscle activation and adjustments of timing and force, movements require elements of perceptual processes and cognitive control of action (Willingham et al., 1998; Rizzolatti and Luppino 2001; Buch et al. 2010; Duque et al. 2013; Kennerley et al. 2004; Ridderinkhof et al. 2004; Rushworth et al. 2004; Rushworth et al. 2005). It is important to highlight at this stage that while psychomotor disturbances encompass a broad range of signs and symptoms in BD from catatonia, neurological soft signs (NSS), medication induced extrapyramidal symptoms (EPS), psychomotor agitation and slowing, the term 'psychomotor functioning' has been used in this thesis to describe the contribution of all the cognitive and motor processes involved in movements. In this light, many cognitive abnormalities present in BD may be directly related to the processes involved in motor functioning.

As psychomotor abnormalities have been linked to reduced functional outcome (Martinez-Aran et al., 2004; Tabares-Seisdedos et al., 2008), it was essential to further understand different neuro-cognitive processes relating to motor control in individuals with BD. This thesis aimed at identifying underlying mechanisms and sub-processes of psychomotor functioning that are affected in BD, specifically an investigation of impairments that are clinically manifested as psychomotor slowing (reflected as disturbances in planning and execution of a task), and an investigation of cognitive control processes necessary for successful movements, namely inhibition of unwanted behavioral output and performance monitoring.

To investigate psychomotor speed in euthymic BD, experiment 1 (**Chapter 2**) was run. Using a digitized tablet enabled different motor and cognitive sub-processes involved in speeded movements to be measured. As hypothesized, individuals with BD in a euthymic state had more psychomotor slowing than healthy controls. Specifically, there was a slowing of cognitive processes relating to movement, while neuro-motor processes were spared. Although this study was able to successfully

differentiate between motor and cognitive components of a movement, unfortunately this method did not enable a determination of which stages of cognitive processing relating to movements were impaired.

To gain a better understanding of neuro-cognitive processes underlying psychomotor behavior in BD, further investigations were conducted on neurobiological mechanisms underlying response inhibition and performance monitoring, two components of executive functioning which are associated with movement execution, and thus psychomotor activity (**Chapters 3, 4 and 5**). A systematic literature review of available event-related potential (ERP) data during cognitive tasks in euthymic BD (**Chapter 3**) highlighted abnormalities in brain activity in individuals with BD compared with healthy controls at various stages of information processing. Using electrophysiology in conjunction with an easy task (**Chapter 4)**, individuals with BD demonstrated normal inhibitory behavior together with abnormal ERP activation. Specifically, patients had marginally reduced NoGo N2 amplitudes, an early ERP measure of conflict detection and increased NoGo P3 amplitudes, indicating an overactivation of cortical fronto-central areas when inhibitory control is necessary. In other words, BD patients require more effort to inhibit behavior, which may lead to difficulties in inhibition when tasks are difficult. In addition to abnormal inhibitory processing, a following study (**Chapter 5**) demonstrated reduced Error Related Negativity (ERN) amplitudes (reflecting reduced activity in the anterior cingulate cortex (ACC)) when residual depressive symptoms were controlled for, reflecting reduced performance monitoring in BD.

An updated literature review and critical appraisal of evidence-based trials of pharmacotherapy in BD was presented (**Chapter 6**), highlighting that current treatments are solely targeted towards stabilizing mood, while consideration of cognitive and motor abnormalities is greatly lacking.

How do the results contribute to understanding the pathogenesis of BD?

With an increased interest in cognitive dysfunction in BD, results presented in this thesis contribute to the knowledge relating to abnormal psychomotor functioning in euthymia. While psychomotor slowing has previously been confused with reduced information processing speed or motor speed, the current investigations were based on a much broader definition of what constitutes psychomotor functioning, namely all of the motor and cognitive processes involved in a movement, from planning, programming, initiation, execution and monitoring a movement. Separating strictly motor from cognitive components (**chapter 2**) and the inclusion of inhibitory control (**chapter 4**) and performance monitoring (**chapter 5**) in the context of psychomotor functions in BD largely extends current knowledge relating to underlying processes relating to observed psychomotor abnormalities in BD.

Thus, abnormalities of different sub-processes underlying movement in BD may explain different clinical presentations of psychomotor activity in BD. For example, execution of a movement can be slowed as a result of reduced information processing speed or as a result of difficulties in detecting conflict in the brain, as this may cause irrelevant/inappropriate stimuli to be extremely distracting. On the other hand, difficulties in performance monitoring or difficulties in inhibition can have an opposite behavioral effect with more impulsive behavior together with errors along the way. These psychomotor abnormalities, regardless of slowed or impulsive movements have implications for functional outcome impacting all actions of the individual, including motility, mental activity, and speech.

Although qualitative disturbances of movement may be observed in BD (for example when movements go wrong, or new motor symptoms arise such as tremor, stereotypy or mannerisms), psychomotor slowing is quantitative in nature and may not be clinically present in a prominent fashion. In fact, individuals with BD in a euthymic state do not typically present with obvious clinical manifestations of

psychomotor slowing during daily activities, such as grasping or moving a cup, dressing, tying shoelaces or putting on makeup. This is likely the reason that psychomotor activity in BD is understudied. Nevertheless, using quantifiable measures, deficits associated with psychomotor functioning can be sub-clinically measured. The broadened definition of psychomotor functioning which has been used in this thesis indicates that in addition to neuropsychological evidence of slowed processing speed and motor slowing in euthymic BD (see Correa-Ghisays et al., 2017), a number of different underlying components are disturbed in euthymia specifically, cognitive slowing interfering with initiation of a movement, abnormal inhibition of unwanted behavioral output, difficulties in error detection and monitoring behavior (**Chapters 2,4,5**). These may all lead to abnormal movements and may be related to the BD pathophysiology. This contribution into the pathophysiology of BD is critically important as continuing to increase understanding of abnormalities relating to the disorder (even those that are not easily observed) can help identify new treatment targets that can improve the outcome of the disorder. Implications for treatment development are further discussed below.

Neural circuitry involved in psychomotor functioning in BD

In the search for neural pathways underlying psychomotor functioning, reciprocal connections between the cerebellum/basal ganglia and frontal cortex (mediated by the thalamus) have been proposed to coordinate and sequence motor and cognitive information (Andreasen 1998; Alexander 1986). This circuit was initially referred to as the cortico-cerebellar-thalamic-cortical circuit (CCTCC) and later referred to as the cortical-striatal-thalamo-corical network (CSTC) (see Peters et al 2016 for review). This proposed framework involved in psychomotor functioning has been referenced in many psychiatric disorders including BD (Nauta et al., 1974; Peters et al., 2016). The classical description of the CSTC model posited a few functionally separate loops working in parallel each responsible for different perceptual, cognitive, emotional

and motor aspects relating to motor functioning, including a sensory loop from the sensorimotor cortex, a limbic loop from the medial and orbitofrotal cortex and anterior cingulate cortex, a motor loop from the motor cortex and an executive loop from the dorsolateral prefrontal cortex. Figure 1 provides a simplified scheme of the CSTC network. Each functionally separate loop has different connectivity patterns with the striatum/basal ganglia and the thalamus (See Figure 2).

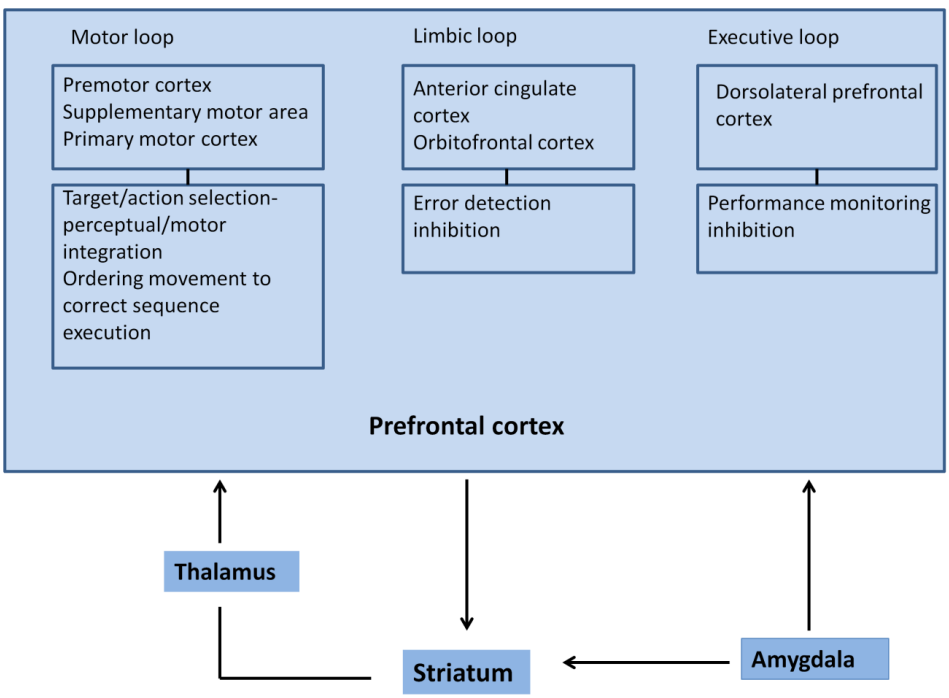

Figure 1: This figure illustrates a simplified scheme of the psychomotor neural network proposed, the cortical-striatal-thalamo-corical network (CSTC). Three cortical-striatal loops are illustrated, whereby different regions of the prefrontal cortex responsible for cognitive, emotional and motor aspects relating to motor functioning work in parallel of one another, sending information to the striatum which in turn sends information back to the prefrontal cortex via the thalamus. This circuit has been proposed to coordinate and sequence motor and cognitive information. Emotional input (from the amygdala) is provided at the sub-cortical level (striatum or thalamus) and interacts with motor and control regions.

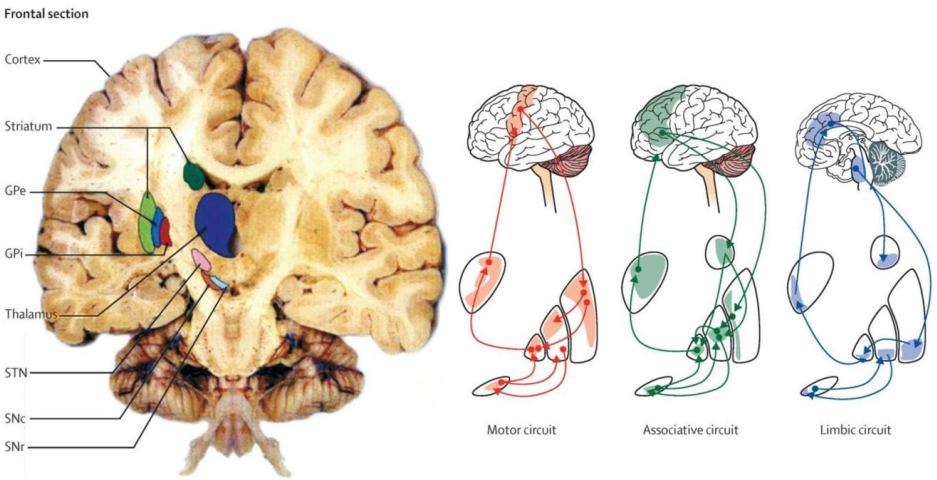

Figure 2: This figure illustrates the different complex connectivity patterns from the cortex to the striatum/babsal ganglia within the different loops; the motor circuit, the executive circuit (associative circuit) and the limbic circuit (Obeso et al., 2014).

However, smoothly executed behavior requires a combination of input from emotional, cognitive and motor cortical areas working together. Therefore, more research has revealed that while these loops may work in parallel of one another, there may also be co-activity between the cortical regions as well as cortico-cortical connections within the prefrontal cortex (including the dorsolateral prefrontal cortex (DLPFC) to premotor regions) (Peters et al., 2016). For example, motor tasks involve the motor loop and additionally require executive control, thereby co-activating the dorsolateral prefrontal cortex (van der Fels et al., 2015). It has also been proposed that in order for information to flow between the circuits, interconnections between the prefrontal regions occur at the level of the striatum which cross the functional boundaries thereby integrating information across the regions (Haber 2016).

Abnormal activity in this circuit would result in a disruption of cognition, perception and motor behavior where deficits can emerge in any domain.

Focusing on the frontal structures, a common neural circuit involving the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Kerns et al., 2004; van veen and Carter 2006; Lavric et al., 2004**)** has been implicated in performance monitoring and inhibitory processes. When an error or conflict is detected, the ACC is activated and calls upon additional recruitment of effort via control resources in the prefrontal cortex. Reduced ACC and DLPFC activity have also been associated with psychomotor slowing in MDD (Narita et al, 2004), suggesting that this circuit plays an important role in the execution and control of movements.

Results presented in the thesis demonstrated reduced ERN amplitudes (**Chapter 5**) and reduced NoGo N2 amplitudes in euthymic BD (**Chapter 4**), reflecting reduced ACC activity in BD and abnormal error or conflict detection. These results are critically important as they extend current knowledge regarding ACC activation in BD. Increased NoGo P3 amplitudes were additionally found (**Chapter 4**) reflecting abnormalities in the prefrontal cortex. In other words, an aberrant ACC-PFC circuit was demonstrated in BD. Based on interconnections between the DLPFC and motor control there are implications of this aberrant circuit for psychomotor functioning in BD. While timing and force do not seem to be affected (**Chapter 2**), executive control processes which are important for planning of movement sequences, task switching, response inhibition, performance monitoring, and error detection greatly affect psychomotor speed.

Although there is evidence in the literature suggesting that both the ERN and NoGo N2 are generated in the ACC (Van Veen and Carter 2002; Bekker et al., 2005)**,** there is an ongoing debate as to whether these ERP components reflect the same underlying process (Yeung et al., 2004). The NoGo N2 is believed to reflect an early process relating to inhibitory control (Bokura et al., 2001**)** but a few different suggestions of its specificity have been given, namely conflict detection, conflict monitoring or response activation (Krakowsky 2016). Based on the data presented in

the thesis (**Chapters 4,5**), the reduction of both ERN and NoGo N2 amplitudes in BD suggest that there may be a common underlying generator for these two components in BD. However, this may not be the case for all patient groups. For example, studies investigating individuals with schizophrenia have demonstrated reduced ERN amplitudes, without a reduction of NoGo N2 amplitudes (Weisbrod et al., 2000; Olvet and Hajcak 2008)**,** suggesting that perhaps these components do not arise from the same underlying process. Whether or not the ERN and NoGo N2 reflect the same process thus remains unclear. Results of the studies presented in the thesis (**Chapter 4,5**) could not resolve the controversy, nor was it the aim of the thesis, however regardless of the exact process they reflect, there appears to be an abnormality in the functioning of the ACC-PFC circuit in BD.

It is imperative to discuss the influence of emotion on the CSTC model especially as difficulties in emotion processing and regulation lie at the core of BD (Phillips and Vieta, 2007; Johnson et al., 2007; Gruber, 2011). According to the CSTC model (see Figure 1) limbic input (via the amygdala) is provided at the sub-cortical level (striatum or thalamus) and interacts with motor and control regions. Imaging studies have demonstrated that there is a negative functional connectivity between the amygdala and frontal regions (ACC and PFC) (Hairi et al., 2000; Dolcos et al., 2006), thus while one is active, the other is suppressed. In other words, any abnormality in the amygdala will affect the ACC-DLPFC cognitive control loop (and vice versa). Therefore, this CSTC network provides a framework for understanding the modulation of emotional information on cognitive and motor functions and provides a broader perspective in light of emotional, motor and cognitive abnormalities present in BD.

Interestingly, many studies in euthymic BD have demonstrated normal activation of the amygdala during emotional tasks, but abnormally increased activation of amygdala during non-emotional tasks (Townsend et al 2012). This implies that during a non-emotional task individuals with BD are nevertheless influenced by arousal mechanisms (in addition to cognitive mechanisms such as attention) which

may alter performance. The consequences of this are that an emotional response to a stimulus may interfere with cognitive control (specifically demonstrated inhibitory control) as a result of extra demands being placed on attentional resources (Ramos-Loyo et al., 2013). Abnormal activation of the amygdala may therefore be an underlying reason for abnormalities in the neural circuitry responsible for response inhibition and performance monitoring (ACC-PFC loop) in BD, and may consequently contribute to psychomotor abnormalities. It is also possible that an opposite pattern is true, with abnormalities in cognitive control influencing the modulation of emotion in BD, which may explain continued mood instability in euthymia.

How do the findings relate to known abnormalities in individuals with schizophrenia and depression?

Due to clinical similarities amongst individuals with BD, MDD and schizophrenia, it often takes years before correctly diagnosing BD. In addition, the cognitive profile of individuals with BD, schizophrenia and MDD have been shown to be largely similar, with the level of impairments being a little bit more severe in schizophrenia (meta analysis, Bora et al., 2015). Although the aim of the thesis was not to directly compare psychomotor functioning in individuals with different diagnoses (and as such patients with schizophrenia and MDD were not tested in the experiments presented) it can be noted that identifying cognitive abnormalities and corresponding neurobiological markers in BD has the potential to reveal possible differences amongst known abnormalities in MDD and schizophrenia.

Using a categorical approach (based on DSM diagnoses), it is interesting to discuss the results of the thesis in comparison with schizophrenia and MDD. As described in the first experiment (**Chapter 2**), a distinct cognitive slowing without motor slowing in euthymic BD is similar to findings in stabilized patients with schizophrenia (Van Hoof et al., 1998; Jogems-Kosterman, 2004) possibly reflecting cognitive slowing in all psychotic disorders. Motor slowing demonstrated in BD was

only related to residual depressive symptoms and therefore shares similarities with previous reports of both motor and cognitive slowing in MDD (Van Hoof et al., 1998). Similarly, results relating to performance monitoring in BD (**Chapter 5**) also demonstrate that elements of depression and underlying psychotic disorders seem to play a role in euthymic BD. Reduced ERN amplitudes in BD are similar to those seen in patients with schizophrenia (Alain et al., 2002; Bates et al. 2002; Houthoofd et al., 2013) and may be related to an underlying deficit in performance monitoring in all disorders that may present with psychotic features. Moreover, depressive symptoms increased ERN amplitudes in BD, which is in line with depression being linked to heightened awareness of making a mistake as a result of generally seeing things in a negative light. This is reflected in an increased ERN in patients with mild/moderate MDD (Holmes and Pizzagalli 2008; Chiu and Deldin 2007; Ruchsow et al., 2006**).** In other words, results from these studies show considerable overlap across the disorders in their underlying processes.

However, interestingly, results from the study presented on inhibition in BD (**Chapter 4**) may shed some light unto differences in the underlying processing in BD. Individuals with BD displayed normal inhibitory control on a simple task together with abnormal brain activity. While on a behavioral level, studies investigating schizophrenia and MDD also demonstrated normal behavior on an easy task (Go/NoGo task) (Ruchsow et al., 2008; Chun et al., 2013), the neurobiological processes involved during an inhibition task seem to be different in BD from previous findings in MDD and schizophrenia. Patients with BD displayed marginally reduced NoGo N2 amplitudes together with increased NoGo P3 amplitudes (**Chapter 4**) while patients with schizophrenia and MDD (not severely depressed) had normal NoGo N2 together with reduced NoGo P3 amplitudes (Chun et al., 2013; Weisbrod et al., 2000; Ruchsow et al., 2008). Normal NoGo N2 in schizophrenia and MDD reflect intact early stages of conflict detection leaving more resources available for later stages of inhibition. Although this later stage is compromised, it seems as though there are enough resources left to deal with the impairment in an easy task and behavioral

differences might only be present when the task is more demanding. In other words, psychomotor behavior in BD seems to be similar to depression and schizophrenia however, there may be some differences in the underlying processes involved in BD, with a specific difference on the connections between early and late processing relating to inhibition. Importantly, results suggest that BD patients seem to have a different neurobiological pattern relating to inhibition than patients with schizophrenia and depression, shedding light on information processing unique to BD unrelated to mood influences.

Despite the neurobiological differences relating to psychomotor abnormalities suggested between BD, schizophrenia and MDD, it is clear that there is a large overlap between these disorders, with diagnoses failing to capture all biological distinctiveness. Given the neurobiological evidence demonstrating how much BD, schizophrenia and MDD have in common (Craddock and Owen 2005), it is important at this stage to address a major topic of debate in psychiatric research as to whether BD, MDD and schizophrenia represent distinct disorders in terms of their neurobiology (Marneros 2006) or whether they might be better represented using a dimensional approach and viewed on a spectrum of psychiatric illness (Angst et al., 2007). It might be beneficial to identify underlying neurobiological markers as opposed to using categorical diagnoses to differentiate between these similar syndromes.

The Research Domain Criteria (RDoC) initiative (see Cuthbert and Insel 2013) was implemented with the aim of moving away from research that is focused on the traditional view of disorders based solely on a clinical description, but rather to move towards research that is focused on both the behavior and neural systems that are responsible for behavior. The goals of the RDoC initiative are to provide research based on data that is gathered across different levels of analysis (genes, brain circuits, behavioral domains) in order to further understand psychopathology and develop treatment. In this framework, constructs are investigated dimensionally across diagnoses. This framework may tap into factors that mediate the clinical

course and respond to treatment (Yager et al., 2017). Currently, there are five functional dimensions that are included in the initiative; cognitive systems, systems for social processes, negative valence systems, positive valence systems, and arousal/regulatory systems. Unfortunately, motor systems are missing. Given that there are motor dysfunctions in many psychiatric disorders, inclusion of a motor category would be beneficial in providing insight into underlying biology associated with psychopathology (Bernard and Mittal 2015).

Implications for treatment

Pharmacological treatment

There is growing awareness that treatment of BD extends beyond the initial focus of controlling affective symptoms. In order to achieve a more complete recovery, it is important to address all of the challenges which are inherent in this complex disorder. Even when symptomatic improvement is achieved in BD, it has been demonstrated that 20–30% of euthymic patients have impaired social functioning (Ceylan and Oral, 2001) including difficulties with work adjustment, social and leisure activities adjustment and marital adjustment (Bauwens et al., 1998). Cognitive impairment affects occupational and social functioning and the overall quality of life of the patients (Vieta et al., 2002). Despite the great burden of cognitive impairments on functional outcome in BD, with clearly demonstrated abnormalities in psychomotor functioning, the review presented in the thesis on current pharmacological treatment in BD (**Chapter 6)** illustrates the lack of research on pharmacological treatments targeted towards cognitive impairment. No FDA drugs have been approved for the treatment of cognitive deficits in BD. Large controlled studies have investigated treatment options of mood episodes (including the hallmark STEP-BD trial (Sachs et al., 2003)), but the field needs to extend its attention to other critical domains, such as the cognitive deficits associated with BD.

While some currently used pharmacological treatments may indirectly have a protective role on neuro-cognitive functions, others may have side effects such as EPS and neurocognitive effects due to the sedative or blunting mechanisms of medications such as lithium, anticonvulsants, antipsychotics or antidepressants (Sole et al., 2017; Martinez-Aran and Vieta 2015). Despite side effects of treatments, cognitive impairments have been demonstrated in medication free patients indicating that these impairments are related to the illness and cannot be solely caused by medication (Goswami et al., 2009). Mood stabilizers such as lithium appear to have few or minor negative effects on cognition, with perhaps mild adverse effects on psychomotor performance (Wingo et al., 2009). On the other hand, neuro-protective effects of lithium have also been demonstrated (Fountoulakis et al., 2008). Much less research has been conducted on anticonvulsants, with lamotrigine and oxcarbamazepine demonstrating the least neuro-toxicity compared with valproate (Gualieri and Johnson 2006). Antidepressants do not have important documented adverse cognitive effects (Cipriani et al., 2017) and there is evidence from studies in MDD that they may even have beneficial effects in reducing cognitive impairments (Keefe et al., 2014), however this has not been demonstrated in BD. Research points to similar cognitive impairments associated with atypical antipsychotics (quetiapine, olanzapine and risperidone) (see Cipriani et al., 2017; Sole and Jimanez 2015), however there is preliminary evidence of cognitive enhancement with lurasidone in BD (Yatham et al., 2017). It is therefore important for clinicians to also consider the cognitive profile of each drug when treating the affective symptoms in order to minimize the side effects.

There are some hypotheses regarding brain receptors that are involved in psychomotor functioning in BD and can be used for treatment development. Dopamine plays an important role in BD. It has been suggested that patients with BD are not able to maintain homeostatic regulation of dopamine function leading to cyclical changes in dopamine neurotransmission (Ashok et al., 2017). The dopamine hypothesis in BD is well established and the vast majority of current antipsychotics

are dopamine D2 receptor blockers. Importantly, in addition to the role that dopamine plays on mood symptoms it has been suggested that dopamine facilitates the communication in the CSTC network that has been proposed to be involved in psychomotor functioning (Nauta et al., 1974), with ACC functioning supported by input from the dopamine system, which then carries signals that mediate related but distinct functions (see Paus 2001). Dopamine is therefore important for motor and cognitive abnormalities observed in BD, affecting selection and execution of behavior (Holroyd and Yeung 2012), and is an essential neuromodulator of performance monitoring (Holroyd and Coles 2002). Antipsychotics, which block dopamine, may cause or exasperate impairments in psychomotor speed which has been demonstrated (see Sanchez et al., 2014; Balanzá-Martínez et al., 2010). In addition, there is evidence that the dopamine system is involved in the generation of ERN, with amphetamine (a dopamine agonist) increasing ERN amplitudes (de Bruijn et al., 2004) and haloperidol (a dopamine antagonist) reducing ERN amplitudes (de Bruijn et al., 2006).

Although there is the most evidence for the role of dopamine in psychomotor functioning, there is also evidence to suggest the involvement of serotonin and GABA receptors (review Jocham and Ullsperger 2009). Serotonin has been shown to mediate post error slowing and SSRI administration was shown to be beneficial for control over movement (Fischer et al., 2015). This has important implications for psychomotor functioning as antidepressants given in BD may be beneficial for control of movements.

In addition, it has also been proposed that the inhibitory connection between the amygdala and PFC is modulated by GABAergic interventions (Cunningham et al., 2002). While GABA inhibits the connections, it is synthesized from the excitatory neurotransmitter glutamate. By facilitating the coordination of cortical activity, GABA may influence cognitive processing (Wang et al., 2011) as may the NMDA glutamate receptor (Brady et al., 2013). Abnormally elevated GABA levels in the ACC in euthymic BD has been demonstrated (Brady et al., 2013), as well as elevated

glutamate in euthymic BD (Ehrlich 2015). Interestingly, glutamate hyper-function via GABAergic pathways has been linked to catatonia symptoms in schizophrenia (Northoff et al., 1997). This is important to note as catatonia is in fact most frequently present in BD (Taylor and Abrams 1973). GABA-modulating medication (benzodiazepines, anticonvulsants) reduced GABAergic dysfunction in the ACC as well as catatonic symptoms (Northoff et al., 1997). Results from the studies in this thesis implicated a reduction of ERP amplitudes as a result of benzodiazepine use (**Chapters 4 and 5**), confirming other previous reports (Riba et al., 2005; de Bruijn et al., 2004). Therefore, differences in the GABAergic system may also contribute to cognitive deficits in BD (Bearden et al., 2010). Lithium is the most effective and well established treatment of BD and has been the standard pharmacological treatment for BD for over 70 years (Malhi et al., 2016). It has a broad range of effects that unfortunately remain unclear, however amongst them lithium modulates neurotransmission (dopamine, glutamate and GABA). In other words, the role of dopamine, serotonin and GABA on the modulation of execution of movement may be considered to determine which should be targeted for improved psychomotor functioning.

In recent years, BD has been proposed to be an illness with progressive neural deterioration (Malhi et al., 2016), which has been termed 'neuro-progression'. While more research is needed in this regard, it has been argued that BD may be a combination of neurodegenerative processes or neurodevelopmental process (fixed) (Cipriani et al., 2017). Inflammatory changes have been observed in BD (Kapczinski et al., 2011; Magalhães et al., 2011). Inflammation is an immune response following injury to the neuronal environment. It has been proposed that following an acute episode, neuronal injury may trigger inflammation which in turns activates microglial cells. This modifies the synaptic environment (through influencing synaptic formation and the reduction of overall number of neurons and synapses) in order to cope with the injury. After a few episodes, an excessive production of pro-inflammatory cytokines causes the microglia to be in a constantly activated state which potentially

leads to systemic toxicity (see Stertz et al., 2013). As cognitive deficits can be influenced by inflammatory mediators (through the shaping of synaptic transmissions), immune system abnormalities may provide the link between progressive dysfunction, cognitive impairments and medical co-morbidities (specifically inflammatory disorders, metabolic syndrome) present in BD (Goldstein et al., 2009). There is preliminary evidence that mood stabilizers such as lithium modulate neuro-inflammation (Kang et al., 2012; Nahman et al., 2012; Zhang et al., 2012; Malhi and Outhred 2016), however there is not yet enough evidence to support the neuro-protective effects. Newer research into the adjunctive use of drugs with anti-inflammatory properties (for example omega-3 acids)(Torrey and Davis 2012) has demonstrated that these drugs might be beneficial for ameliorating depressive symptoms but not mania. Although microglial activation and its role in BD are not completely understood, it has been suggested that there is an important role of inflammatory components in the pathophysiology of BD (Stertz et al, 2013) and targeting treatment towards neuroinflammation may have important benefits for cognitive deficits in BD, and may be beneficial in the prevention of the development of neurodevelopmental disorders such as Alzheimers and Parkinson's disease (see Forlenza et al., 2014).

Inflammation also impacts other transmitter systems. The presence of a pro-inflammatory state leads to increased consumption of tryptophan. Quinolinic acid, a tryptophan catabolite acts as an agonist on the N-methyl-D-aspartate (NMDA) receptor causing neuro-toxic effects (through receptor over-activation) (Stone and Perkins, 1981; Schwarcz et al., 1983). Moreover, quinolinic acid causes elevated glutamate concentrations (Tavares et al., 2002). Kynurenic acid (KYNA) is a tryptophan metabolite that acts as an antagonist on the NMDA glutamatergic receptor and on the nicotinergic receptor (Hilmans et al., 2001). It inhibits glutamatergic transmission and modulates midbrain dopamine activity (Nilsson et al., 2006). Interestingly, KYNA has been demonstrated to be elevated in euthymic BD (Ollson et al., 2010) thereby influencing glutamatergic and dopaminergic

neurotransmission in BD. Elevated KYNA in BD may contribute to cognitive decline in BD (Robbins and Murphey 2006). Neuroprotection may be considered as a therapeutic target in BD.

Non-pharmacological treatment

In addition to implications on pharmacological treatment strategies, cognitive and functional remediation therapy is also an important treatment strategy in BD (see Bowie et al., 2013; Sole et al., 2017). This is an intervention based on improving psychosocial functioning including tackling neuro-cognitive deficits through training the brain to learn compensatory and new adaptive strategies. This form of neuropsychological rehabilitation may show promise, with evidence from two meta-analyses demonstrating improved cognitive functions in schizophrenia when combined with psychiatric rehabilitation (Wykes et al., 2011; McGurk et al., 2007). More research is necessary to determine its efficacy in BD. In one small study, executive functioning and occupational status improved after sessions of cognitive remediation. However, no control group was used in this study, making it difficult to generalize the findings (Deckersbach et al., 2010). Results in the thesis may suggest that in order to improve psychomotor functioning, cognitive remediation needs to address numerous underlying cognitive processes.

In addition, a lack of awareness of clinical and cognitive abnormalities present are consistent features of psychotic disorders ('loss of insight') and have been linked with neuro-cognitive decline in BD (Nair et al., 2013, Van Camp et al., 2016). It may be beneficial to target this issue of insight with functional remediation in order to improve cognition in BD.

Campanella and colleagues (2013) highlight the benefit of using ERP profiles for treatment in combination with medication and psychotherapy. They suggest that by using ERP profiles, specific cognitive deficits can be identified in patients allowing the psychiatrists to develop individualized, targeted treatment. Moreover, individual

treatment plans can eventually combine pharmacotherapy, psychotherapy and ERP-oriented cognitive rehabilitation (see **Chapter 3**) in order to have the most beneficial treatment and aid functional recovery. As discussed in **chapter 3**, cognitive remediation can include targeted brain stimulation techniques (rTMS or tDCS) to normalize brain activity, with recent evidence of increased ERP activity in euthymic BD following tDCS (Bersani et al, 2015).

Individual differences in overall cognitive reserve have been demonstrated suggesting that some individuals have a greater capacity to endure neuropathology and will have less clinical manifestations of cognitive decline (Stern 2009). As BD also shows neuro-degenerative properties, with increased cognitive decline with each episode, it is critical to implement interventions during early stages of the illness to improve overall functioning. This includes pharmacological treatment to prevent episodes, treatments of subclinical mood symptoms, cognitive/functional remediation and/or non-invasive treatment of cognitive impairments. In addition, interventions aimed at increasing cognitive reserve early in the course of the illness (such as education and lifestyle changes) may minimize neuropsychological deficits (Martinez-Aran and Vieta 2015).

Limitations of the research

Findings in the thesis have to take into account some limitations. A first limitation of the studies is that many clinical aspects may have an effect on cognition. For example, duration of illness, the number and types of episodes and previous psychotic episodes have been shown to influence cognition in BD (Martinez-Aran et al., 2004; Zubieta et al., 2001). In fact, one study using individuals with BD who were euthymic for many years demonstrated that executive functioning worsened as the illness progressed (Torrent et al., 2012), further highlighting degenerative aspects of BD. Attempts in the present studies (**Chapters 2,4,5**) were made to control for the most probable clinical variables relevant to the studies, unfortunately, not all clinical

variables were controlled for (for example, age, premorbid IQ, co-morbidities) and these influences need to be considered.

A second limitation in the studies is that all of the patients who participated in the studies were being treated with a range of different medications. The studies did attempt to control for effects of medication status (**Chapters 2, 4, 5**), however, given the heterogeneous medication regimen across patients, with many patients taking several combinations of drug treatments at varying doses, it is extremely difficult to make inferences about the effects of specific medications on cognition and need to be interpreted with caution. As it is unethical to discontinue treatment this remains an important limitation in all research of BD.

In addition, greater impairments and more ERP abnormalities seem to be present in patients with a history of psychotic symptoms. For example, there is evidence of greater executive functioning impairments (Glahn et al., 2007) and sensory gating abnormalities relating to psychosis (**Chapter 3**). It has been proposed that psychotic BD may be a distinct phenotype of BD (Brissos et al., 2011), and needs to be investigated separately. While the individuals with BD investigated in the present studies (**Chapters 2, 4,5)** were all in a euthymic state and therefore by definition not psychotic, the present studies included both patients who experienced previous psychotic episodes and those who did not. It is debatable whether past psychotic episodes influence cognition during the euthymic stage of the illness. In our study ERN amplitudes were not different based on history of psychosis (**Chapter 5**).

A further limitation is that the individuals with BD in the studies presented did not have residual hypomanic symptoms, and therefore an analysis of the effects of residual hypomania was not conducted. This is important to investigate since impulsivity is an observable phenomenon in mania and the contribution of these mood symptoms on difficulties in inhibition and performance monitoring needs to be further understood.

Future research

Residual mood symptoms are common during euthymia (Angst et al., 1980) and they are also related to impaired quality of life, and recurrences of mood episodes in BD (Perlis et al., 2006). Although the individuals with BD investigated in the experiments presented in the thesis were in a euthymic state, residual depressive symptoms amongst the patient samples clearly played a role on psychomotor functioning. Depressive symptoms in BD increased neuro-motor slowing (**Chapter 2**), increased ERN amplitudes (**Chapter 5**) and correlated with NoGo N2 and NoGo P3 amplitudes in BD (**Chapter 4**). These findings are in line with known influences of depressive severity on ERP relating to inhibition and performance monitoring. For example, patients with MDD with severe depressive symptoms have enhanced (more negative) NoGo N2 amplitudes as opposed to reduced NoGo N2 amplitudes in less severe depression (Zhang et al., 2007). In addition, severely depressed MDD patients have reduced NoGo P3 amplitudes and abnormal behavior. This pattern suggests that depression leads to a heightened awareness of conflict occupying available resources, leaving limited resources available for the later stage of inhibition which is compromised. As a result, behavioral abnormalities arise. Furthermore, patients with extremely severe MDD do not show increased ERN amplitudes as opposed to moderately severe MDD patients (Schrijvers et al, 2008; Chiu and Deldin 2007). It is possible that melancholic depression manifests itself in learned helplessness as opposed to self-critical thoughts and a strong sensitivity to errors reflected by a reduction of ERN amplitudes. In other words, depressive symptoms play an important role in psychomotor activity, both in motor components as well as in the early stage of inhibitory processing (conflict detection) and performance monitoring. It is therefore critically important for future studies investigating underlying processes of cognitive deficits in BD to take into consideration residual mood symptoms as these state related symptoms may confound results. In addition, the fact that depressive symptoms play such an important role on cognition in BD further

highlights the benefits of using a dimensional approach in research using symptoms in addition to DSM diagnoses.

As discussed in the review on ERPs in BD (**chapter 3**), there are a number of ERP abnormalities present in euthymia that arise at different stages of information processing and are independent of one another including abnormalities relating to early stages of information processing and attention. There is clearly an advantage in using simple tasks in the investigation of underlying neural processes relating to psychomotor functioning in BD (by limiting the amount of cognitive sub-processes that are necessary for the task). Nevertheless, even simple tasks are not able to completely segregate specific cognitive sub-processes and may include some elements of other cognitive processes, such as attention. In addition, behavioral outcome of movements depends on the amount of cognitive resources that are allocated to each specific process involved. For example, there is a close link between attention allocation and manual response execution (Eimer et al., 2005; Norman and Shallice 2000). Attention allocation plays an important role in all executive functions. As the limited capacity of attentional resources get used up, few resources remain for later stages of cognitive processing. While this may not be directly observable in easy tasks as attentional load is low, problems may arise when tasks are more difficult. In support of this, Stock (2016) found that Go P2 activity (which reflects the amount of attention given to a task at an early stage of information processing) predicted inhibitory behavior more so than later stages of NoGoN2 and NoGoP3. The implications of this in the context of the present thesis are that behavioral outcomes requiring response inhibition or performance monitoring are likely to depend on the amount of cognitive resources that are allocated to earlier stages of stimulus and response activation. Therefore, it would be interesting for future studies to directly manipulate attention by varying attentional load, allowing further investigations into different components relating to psychomotor functioning such as inhibitory processes and performance monitoring.

In addition and as suggested, psychomotor abnormalities may arise via disturbances in the neural pathway from the amygdala. This has important implications, for example it is possible that treating residual depressive symptoms and difficulties in emotion regulation will in itself enhance cognitive and psychomotor abnormalities. In the search of further understanding cognitive deficits and the underlying neurobiological correlates in BD, there is a need to examine the functional connectivity (with resting-state fMRI) between the amygdala and the ACC-DLPFC circuit during non emotional tasks.

Results from this thesis extend current knowledge relating to impulsive behavior in BD by providing important data on how individuals with bipolar disorder in a euthymic state inhibit unwanted responses and manage errors. In an attempt to further understand underlying processes relating to the production of intended responses, it may be interesting to further investigate the Lateralized Readiness Potential (LRP) in BD, an ERP that is thought to reflect the activation of response-related processes following stimulus processing (Coles 1989) as a measure of motor preparation (Sanders 1980), allowing more insight into psychomotor slowing in BD. In addition, while EEG is directly linked to neuronal electrical activity with millisecond precision, there is low spatial resolution relating to underlying cortical activity. Linking ERP findings of psychomotor functions in BD with imaging (using single-trial EEG informed fMRI analysis; Debener et al., 2006) can further pinpoint neural dynamics of cognitive processes with high spatial and temporal resolution.

Conclusion

Psychomotor abnormalities are prominent clinical features in BD. The definition of psychomotor functioning in BD has been broadened to include not only motor speed or processing speed but additionally all processes involved in a movement, including inhibition and performance monitoring. This has allowed an in-depth investigation into underlying mechanisms and sub-processes relating to psychomotor

abnormalities in euthymic BD, where research has been lacking. The inclusion of inhibition and performance monitoring as part of the psychomotor construct has important implications for treatment targets, as these underlying deficits may interfere with functional outcome.

Importantly in the search of underlying neurobiological processes relating to psychomotor functioning in BD, results of the thesis go a long way to resolve contradictory results regarding ACC involvement in BD. Using electrophysiology, a direct investigation of ACC activity demonstrated reduced ERN amplitudes and NoGo N2 amplitudes suggesting reduced ACC activation in BD. Furthermore, additional increased cortical activity extends to an abnormal ACC-DLPFC cognitive control circuit. This extends knowledge relating to information processing capacities in BD whereby equal performance in BD requires more effort.

More efforts should be aimed at targeting these underlying processes which together manifest clinically as psychomotor abnormalities. In addition to targeting mood symptoms, improving cognitive and psychomotor symptoms may improve overall functional outcome of the patients.

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Chapter 8

Summary

Apart from mood episodes, cognitive deficits are critical features of bipolar disorder (BD), persisting in euthymia, and interfering with overall functioning of the individuals. In addition to affective and cognitive symptomatology, psychomotor abnormalities are prominent clinical features in BD also linked to the functional outcome of the individuals. Psychomotor disturbances in BD have only been investigated using simple measures relating to motor speed or processing speed. However, movements involve numerous underlying cognitive processes ranging from motor selection, planning, preparation, motor programming, initiation, task switching, response inhibition, error detection and performance monitoring, whereby dysfunction at any stage can result in disturbed psychomotor functioning. Therefore, the term 'psychomotor functioning' has been used in this thesis to describe the contribution of all cognitive and motor processes involved in movements. As such, many cognitive abnormalities present in BD may be directly related to processes involved in motor functioning.

The purpose of this thesis was to identify underlying mechanisms and sub-processes of psychomotor functioning that are affected in euthymic BD. More specifically, an investigation was conducted of impairments that are clinically manifested as psychomotor slowing (reflected as disturbances in planning and execution of a task) in addition to an investigation of cognitive control processes necessary for successful movements, namely inhibition of unwanted behavioral output and performance monitoring.

Chapter 2 presented a behavioral investigation of psychomotor slowing in BD. A group of individuals with BD in a euthymic state were compared with matched healthy controls on drawing tasks with varying levels of difficulty using a digitized writing tablet. Movement time (MT), reflecting fine motor processing, and initiation time (IT), reflecting cognitive processing of visual-spatial information were separately measured in each group. This behavioral method has not previously been used in BD and allows cognitive and motor component of a movement to be distinguished from one another in order to further understand the nature of psychomotor slowing

present in BD. Individuals with BD demonstrated longer ITs and comparable MTs in the most simple task, providing evidence for overall psychomotor slowing in BD, specifically in the cognitive component of movement. In addition, longer MTs reflecting a slowed motor component of movement were present in BD when the cognitive load was high (in the complex drawing task) and when residual depressive symptoms were present. These findings extend current knowledge of the nature of psychomotor slowing in BD.

Although this study was able to successfully differentiate between motor and cognitive components of a movement in BD, unfortunately this method did not enable a determination of which stages of cognitive processing relating to movements were impaired. **Chapter 3** introduces the usage of electrophysiological measures to further understand neurobiological correlates underlying abnormal behavior. Event related potentials (ERP) during the performance of a task reflect information processing during distinct cognitive stages. A systematic literature review and critical evaluation of the available ERP data in euthymic BD was conducted, relating to differences in sensory processes, attention, inhibition and performance monitoring compared with healthy controls. The review focused on the functional significance of abnormal ERP activity present in BD and examined clinical and medication influences on the ERP. ERP differences in BD arise at various stages of cognitive processing, specifically in early auditory and visual processing, attention allocation, context updating, inhibition and performance monitoring. However, ERP differences vary with stimulus factors and clinical profile. Treating these deficits and their underlying neurobiological disturbances corresponding to abnormal performance on cognitive tasks may aid functional remission. This knowledge might enable personalized treatment interventions targeting specific cognitive deficits.

Thus, the ERP methodology can be used to gain a better understanding of neuro-cognitive processes underlying psychomotor behavior in BD. Investigations of cognitive control processes necessary for successful movements were carried out, specifically, inhibition of unwanted behavioral output and performance monitoring.

Chapter 4 provided an investigation of two ERP components reflecting sub-processes of inhibition, the NoGo N2 (generated in the anterior cingulate cortex (ACC) and inferior frontal cortex) and NoGo P3 (generated in the orbitofrontal cortex), as this had not yet been investigated in BD. Individuals with BD are reported to have difficulties with inhibition, even in a euthymic state. However, in the search for underlying neurobiological correlates of inhibitory control in BD, the literature on cortical activity associated with response inhibition in BD remains ambiguous. Individuals with BD in a euthymic state and matched healthy controls performed a Go/NoGo task and the ERPs reflecting inhibitory control were compared. Individuals with BD demonstrated marginally reduced NoGo N2 amplitudes and increased NoGo P3 amplitudes compared with healthy controls when patients using benzodiazepines were excluded from the study. No behavioural differences between the groups were found. Reduced NoGo N2 amplitudes in BD reflect aberrant conflict detection, an early stage of the inhibition process. In addition, increased NoGo P3 amplitudes in BD despite normal task performance reflect an overactive cortical system during a simple inhibition task. Difficulties in early stages of inhibition in BD appear to have been compensated by increased cortical activation. This study extends current knowledge regarding cortical activations relating to inhibitory control in BD.

In **Chapter 5,** performance monitoring, an important aspect of executive functioning was investigated in euthymic BD. Performance monitoring involves continuous monitoring of behavior and making subsequent behavioral adjustments when an error is made. A well known electrophysiological marker for performance monitoring is the error-related negativity (ERN) or the error negativity (Ne), generated in the ACC during the production of errors. Although a lot of attention has been given to the underlying neural underpinnings relating to performance monitoring in other major psychiatric disorders, there is little information regarding performance monitoring using ERN in BD. In addition, there is conflicting evidence regarding the role of the ACC in BD. This was the first study to date to investigate performance monitoring as reflected in the ERN in euthymic BD. Individuals with BD

in a euthymic state were compared with matched healthy controls on a speeded two-choice reaction-time task (the Flankers task) in conjunction with electrophysiological measures. Reduced ERN amplitudes were demonstrated in euthymic BD compared with healthy controls when controlling for residual mood. These results reflect reduced performance monitoring in BD and extend current knowledge of executive functioning in BD. Importantly, these results go a long way to resolve contradictory results regarding ACC involvement in BD as residual mood symptoms appear to influence error related ACC activation.

Chapter 6 provided an updated comprehensive review and evaluation of the available evidence-based trials of pharmacotherapy for the treatment of BD I**.** BD I is complex with a chronic course that significantly impacts a sufferer's quality of life. As of right now, there are many available treatments that aim to rapidly treat manic or depressive episodes and stabilize mood. Stabilization includes preventing relapse of a mood episode or reducing the frequency of episodes or the severity of symptoms (and subthreshold symptoms) in order to enhance social and occupational functioning. However, treatment remains a challenge due to the complexities of BD. This chapter reviewed randomized active comparator-controlled or placebo-controlled trials evaluating the use of current pharmacotherapy in adults with BD I from phase III to clinical practice. Monotherapy and combination therapy for acute and long-term treatment were reviewed for this purpose. It was demonstrated that there are many treatments available for BD mania; however, the depressive and stabilization phases of the illness remain a clinical challenge. This review highlights that current treatment strategies are targeted towards rapidly treating acute manic or depressive episodes and stabilizing mood and not on cognitive or motor abnormalities. However, research efforts must also focus on treating cognitive impairment, which adds to lower functional outcome and there is dire need for new, more targeted treatments in BD I, with a critical view of the side effects.

In **Chapter 7,** the implications of the studies are discussed. The definition of psychomotor speed in BD has been broadened to include not only motor speed or

processing speed but additionally all processes involved in a movement, including inhibition and performance monitoring. This has allowed an in-depth investigation into underlying mechanisms and sub-processes relating to psychomotor abnormalities in BD, where research has been lacking. The inclusion of inhibition and performance monitoring as part of the psychomotor construct has important implications for treatment targets, as these underlying deficits may interfere with functional outcome.

Importantly in the search for underlying neurobiological processes relating to psychomotor dysfunctioning in BD, results of the thesis go a long way to resolve contradictory results regarding ACC involvement in BD. Using electrophysiology, a direct investigation of ACC activity demonstrated reduced ERN amplitudes and NoGo N2 amplitudes suggesting reduced ACC activation in BD. Furthermore, additional increased cortical activity extends to an abnormal cognitive control circuit. This extends knowledge relating to information processing capacities in BD whereby equal performance in BD requires more effort. Future research should be aimed at understanding these underlying processes which together manifest clinically as psychomotor abnormalities. In addition to targeting mood symptoms, improving cognitive and psychomotor symptoms may improve overall functional outcome of the patient.

Chapter 9

Dutch Summary

Behalve van stemmingsepisodes zijn cognitieve tekorten kenmerkend voor bipolaire stoornis (BD). Deze tekorten persisteren in de rustige, oftewel euthyme, fase van BD en interfereren met het algemeen functioneren van individuen. Naast de affectieve en cognitieve symptomen, zijn psychomotorische afwijkingen opvallend aanwezig bij BD en hebben deze eveneens een impact op het functioneren. Psychomotorische stoornissen bij BD zijn voornamelijk onderzocht met eenvoudige meetinstrumenten die motorische snelheid of verwerkingssnelheid nagaan. Echter, bewegingen omvatten verschillende onderliggende cognitieve processen: motorische selectie, planning, voorbereiding, motorische programmering, initiatie, taakomschakeling, respons inhibitie, foutdetectie en prestatiemonitoring, waarbij een dysfunctie in elk van deze processen kan leiden tot een verstoord psychomotorisch functioneren. Om deze reden omvat de term 'psychomotorisch functioneren' in dit proefschrift alle cognitieve en motorische processen die betrokken zijn bij bewegingen. Veel cognitieve afwijkingen bij BD zijn dus direct gerelateerd aan processen die betrokken zijn bij het motorisch functioneren.

Het doel van dit proefschrift was het identificeren van onderliggende mechanismen en subprocessen van psychomotorisch functioneren die aangetast zijn bij individuen met euthyme BD. Meer specifiek werd onderzoek gedaan naar stoornissen die zich klinisch manifesteren als psychomotorische vertraging (weergegeven als stoornissen in de planning en uitvoering van een taak), en naar cognitieve controleprocessen die nodig zijn voor succesvolle acties, met name het remmen van ongewenst gedrag en prestatiemonitoring.

Hoofdstuk 2 beschreef een gedragsonderzoek naar psychomotorische vertraging bij BD. Een groep individuen met BD in een euthyme staat werd vergeleken met gematchte gezonde controles op tekentaken met variërende moeilijkheidsgraden gebruik makend van een gedigitaliseerde schrijftablet. Bewegingstijd (MT), die de fijne motorverwerking weerspiegelt, en initiatie-tijd (IT), die de cognitieve verwerking van visueel-ruimtelijke informatie weerspiegelt, werden afzonderlijk gemeten in elke groep. Deze gedragsmethode werd niet eerder gebruikt

bij BD en maakt het mogelijk om de cognitieve en motorische component van een beweging van elkaar te onderscheiden om de aard van de psychomotorische vertraging in BD beter in kaart te brengen. Ten opzicht van controles vertoonden personen met BD langere ITs en vergelijkbare MTs tijdens de meest eenvoudige taak, indicatief voor een algemene psychomotore vertraging in BD, in het bijzonder voor de cognitieve component van beweging. Bovendien vertoonden de personen met BD langere MTs die een vertraagde bewegingscomponent reflecteerden, met name wanneer de cognitieve belasting hoog was (in de complexe tekentaak) en wanneer er depressieve restsymptomen aanwezig waren. Deze bevindingen breiden de huidige kennis uit over de aard van psychomotore vertraging bij personen met BD.

Hoewel we met deze studie in staat waren met succes onderscheid te maken tussen motorische en cognitieve componenten van een beweging bij BD, was het met de gebruikte methode echter niet mogelijk om vast te stellen welke stadia van cognitieve verwerking tekortkomingen vertoonden.

Hoofdstuk 3 introduceerde het gebruik van elektrofysiologische metingen om neurobiologische correlaten te onderzoeken die ten grondslag liggen aan afwijkend gedrag. Event-related potentials (ERPs) tijdens de uitvoering van een taak weerspiegelen informatieverwerking tijdens verschillende cognitieve stadia. We voerden een systematische literatuurstudie met kritische evaluatie uit van de beschikbare ERP gegevens met betrekking tot verschillen in sensorische processen, aandacht, inhibitie en prestatiemonitoring bij euthyme BD in vergelijking met gezonde controles. De review focuste zich op de functionele significantie van afwijkende ERP activiteit bij BD en onderzocht de klinische en medicamenteuze invloeden op ERPs. Hieruit bleek dat ERP verschillen in BD ontstaan in verschillende stadia van cognitieve verwerking, met name tijdens de vroege auditieve en visuele verwerking, aandachtsallocatie, “context updating”, inhibitie en prestatiemonitoring. ERP-verschillen variëren echter afhankelijk van stimulusfactoren en klinische profiel. Het behandelen van deze tekorten en de onderliggende neurobiologische stoornissen die gerelateerd zijn aan abnormale prestaties op cognitieve taken kan

mogelijk helpen om functionele remissie te bespoedigen. Deze kennis kan bruikbaar zijn met het oog op de ontwikkeling van gepersonaliseerde behandelingsinterventies gericht op specifieke cognitieve gebreken.

De ERP methodologie kan dus gebruikt worden om beter vat te krijgen op neuro-cognitieve processen die ten grondslag liggen aan psychomotorisch gedrag bij BD. Onderzoek werd uitgevoerd naar cognitieve controleprocessen die nodig zijn voor succesvolle bewegingen, in het bijzonder inhibitie van ongewenst gedrag en prestatiemonitoring. **Hoofdstuk 4** beschrijft een onderzoek van twee ERP componenten die deelprocessen van inhibitie reflecteren, de NoGo N2 en NoGo P3, wat dit nog niet eerder met betrekking tot BD werd onderzocht. In een vroeg stadium van het inhibitieproces, ongeveer 200 msec na de presentatie van een NoGo stimulus (wanneer een antwoord moet worden geinhibeerd) wordt een negatieve deflectie in het ERP opgewekt, die conflictdetectie reflecteert en wordt gegenereerd in de anterior cingulate cortex (ACC) en inferieure frontale cortex (IFC). In een later stadium van het inhibitieproces wordt een positieve piek opgewekt rond 300-500 msec na een NoGo stimulus (de NoGo P3), die de werkelijke remming van het motorsysteem reflecteert en wordt gegenereerd in de orbito-frontale cortex. Personen met BD hebben moeite met inhibitie, zelfs in een euthyme staat. Echter, in de zoektocht naar onderliggende neurobiologische correlaten van inhibitoire controle bij BD, blijft er in de literatuur onduidelijk over corticale activiteit die gepaard gaat met responsinhibitie. Personen met BD in een euthyme staat en gematchte gezonde controles voerden een Go/NoGo-taak uit en de NoGo N2 en NoGo P3 werden tussen de groepen vergeleken. Individuen met BD die geen benzodiazepines gebruikten demonstreerden iets kleinere NoGo N2 amplitudes en vergrote NoGo P3 amplitudes in vergelijking met gezonde controles. Er werden geen verschillen in reactietijd gevonden tussen de groepen. Gereduceerde NoGo N2 amplitudes in BD reflecteren afwijkende conflictdetectie, een vroeg stadium van het inhibitieproces. Bovendien reflecteren vergrote NoGo P3 amplitudes in BD, ondanks normale taakprestaties, een corticale hyperactivatie tijdens deze eenvoudige

inhibitietaak. Moeilijkheden in vroege stadia van inhibitie bij BD lijken te zijn gecompenseerd door een verhoogde corticale activatie. Deze studie breidt de huidige kennis uit met betrekking tot corticale activatie gerelateerd aan inhibitieproblemen bij BD.

In **Hoofdstuk 5** werd prestatiemonitoring, een belangrijk aspect van executief functioneren, bij personen met euthyme BD onderzocht. Prestatiemonitoring omvat continue monitoring van gedrag en de daaropvolgende gedragsaanpassingen na het maken van een fout. Een negatieve deflectie wordt opgewekt in het ERP ongeveer 50 tot 100 msec na de fout, bekend als de "error-related negativity" (ERN) of "error negativity" (Ne), en gegenereerd in de ACC. Met andere woorden reflecteert de ERN een vroeg stadium van prestatiemonitoring en ACC activatie tijdens de productie van fouten. Hoewel er veel aandacht is besteed aan de onderliggende neurale basis van prestatiemonitoring bij andere psychiatrische aandoeningen, is er weinig bekend over prestatiemonitoring bij BD gebaseerd op de ERN. Bovendien is de evidentie over de rol van de ACC bij BD tegenstrijdig. Dit was de eerste studie die prestatiemonitoring aan de hand van de ERN in bij euthyme BD onderzocht. De individuen met BD in een euthyme staat werden vergeleken met gematchte gezonde controles op een snelle tweekeuze reactietijdtaak (de Flankers-taak) in combinatie met elektrofysiologische metingen. Individuen met BD in een euthyme toestand vertoonden kleinere ERN amplitudes in vergelijking met gezonde controles wanneer gecontroleerd werd voor stemming. Deze resultaten reflecteren een verminderde prestatiemonitoring bij BD en breiden de huidige kennis uit over het executief functioneren bij BD. Deze resultaten geven een verklaring voor de tegenstrijdige resultaten in de literatuur met betrekking tot ACC activiteit bij BD, aangezien restsymptomen van een depressieve stemming ACC activatie tijdens het maken van een fout lijken te beïnvloeden.

Hoofdstuk 6 omvat een geüpdatete uitgebreide review en evaluatie van de beschikbare evidence-based onderzoeken naar farmacotherapie voor de behandeling van BD I. BD I is een complexe stoornis met een chronisch beloop die aanzienlijke

gevolgen heeft op de kwaliteit van leven. Vandaag de dag zijn er veel behandelingen beschikbaar die er voornamelijk op gericht zijn om manische of depressieve episodes snel te behandelen en stemming te stabiliseren. Stabilisatie omvat het voorkomen van terugval van een stemmingsepisode of het verminderen van de frequentie van de episodes of de ernst van de symptomen (en subklinische symptomen), dit met het oog op het verbeteren van het sociaal en beroepsmatig functioneren. Behandeling blijft echter een uitdaging vanwege de complexiteit van BD. In dit hoofdstuk werden gerandomiseerde gecontroleerde studies of placebogecontroleerde studies geëvalueerd die het gebruik van de huidige farmacotherapie bij volwassenen met BD I van fase III naar de klinische praktijk onderzochten. Monotherapie en combinatietherapie voor acute en langdurige behandeling werden gereviewed. Er werd aangetoond dat er veel behandelingen beschikbaar zijn voor manie. De behandeling van de depressieve episodes en stabilisatiefase van de ziekte blijven echter een klinische uitdaging. Met deze review wordt benadrukt dat de huidige behandelingsstrategieën gericht zijn op het snel behandelen van acute manische of depressieve episodes en het stabiliseren van stemming en niet op de cognitieve problemen. Onderzoeksinspanningen moeten echter ook gericht zijn op het behandelen van cognitieve problemen die bijdragen tot een slechtere functionele uitkomst. Daarnaast is een grote behoefte aan nieuwe, meer gerichte behandelingen in BD I, met een kritisch oog voor de bijwerkingen.

In **hoofdstuk 7** worden de implicaties van de studies besproken. De definitie van psychomotorische snelheid bij BD werd verbreed om niet alleen de motorische snelheid of de verwerkingssnelheid te omvatten, maar bovendien alle processen die bij een beweging zijn betrokken, inclusief inhibitie en prestatiemonitoring. – Dit stond toe een diepgaand onderzoek te verrichten naar de onderliggende mechanismen en subprocessen gerelateerd aan psychomotorische afwijkingen bij BD waar, tot voor kort, onderzoek hierrond ontbrak. De inclusie van inhibitie en prestatiemonitoring als onderdeel van het psychomotorische construct heeft

belangrijke implicaties voor de behandelingsdoelen, aangezien deze onderliggende tekorten de functionele uitkomst kunnen beïnvloeden.

In de zoektocht naar onderliggende neurobiologische processen met betrekking tot psychomotorisch disfunctioneren bij BD, hebben de resultaten uit dit proefschrift bijgedragen tot het verklaren van de tegenstrijdige resultaten met betrekking tot de ACC, Elektrofysiologisch onderzoek van ACC activiteit toonde kleinere ERN amplitudes en NoGo N2 amplitudes aan bij BD, wat hypoactivatie van de ACC bij BD suggereert. Bovendien draagt verhoogde corticale activiteit bij aan een afwijkend cognitieve controle circuit. Dit leert ons over de informatieverwerking bij personen met BD dat gelijke prestaties meer inspanning vergen. Verder onderzoek is nodig om de onderliggende processen die zich klinische manifesteren als psychomotorische afwijkingen beter te begrijpen. Naast de aanpak van stemmingssymptomen kan verbetering van cognitieve en psychomotorische symptomen de algehele functionele uitkomst van patiënten verbeteren.

Appendix

Curriculum Vitae

Personal

Name	Anne Morsel
Date of Birth	17 December 1978
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Education

November 2012- November 2018	PhD Student
	University of Antwerp, Belgium Faculty of Medicine and Healthy Sciences
	Thesis: Hidden beneath the surface of bipolar disorder: cognitive processes underlying movement
	Supervisors: Prof. dr. M. Morrens, Prof. dr. B. Sabbe, Prof. dr. M. Dhar

September 2007- June 2009	MSc in Cognitive Neuropsychology and Neuroscience University College of London, UK Thesis: Combined effects of conflict monitoring and perceptual load on cognitive control Supervisor: Dr. E. Davelaar
September 2003- June 2006	MSc in Psychology Open University, London, UK Thesis: The effects of knowing a child well on contingent control of learning
September 1999- June 2002	BSc in Psychology University College of London, UK Thesis: Focused attention as a necessary condition for change detection Supervisor: Prof. N. Lavie

Academic Experience

- Oral presentation- GGZ congress; University of Antwerp, Belgium
  'Performance monitoring in bipolar disorder', September 2014

- Oral presentation- CAPRI symposium, University of Antwerp, Belgium
  'Performance monitoring, psychomotor functioning and social cognition in bipolar disorder', December 2012

- Poster presentation- CAPRI symposium, University of Antwerp, Belgium
  'Performance monitoring in bipolar disorder: an ERN study' December 2012

- Oral presentation- CAPRI research club, University of Antwerp, Belgium
  'Cognition in bipolar disorder', March 2011

- Poster presentation- Psychiatric Hospital St Norbertus, Duffel, Belgium
  'Performance monitoring in bipolar disorder: an ERN study', March 2011

- European Certificate in Anxiety and Depression, Maastricht University, Netherlands
  Updated expertise on affective pathology, Summers of 2010 and 2011

- Poster presentation, Institute of cognitive Neuroscience London, UK
  'Combined effects of perceptual load and conflict monitoring', September 2009

Publications

Thesis Publications

Morsel AM, Morrens M, Dhar M, Sabbe B (2018). Systematic review of cognitive event related potentials in euthymic bipolar disorder. Accepted for publication in Clinical Neurophysiology

Morsel AM, Morrens M, Sabbe B (2018). An overview of pharmacotherapy in bipolar I disorder. Expert Opinion in Pharmacotherpay, 19(3):203-222.

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