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~~COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER: MAGNITUDE, MODERATORS AND PREVENTION STRATEGIES~~

COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER: TREATMENT AND PREVENTION STRATEGIES

Category: review

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Abstract:

Over the last decade there has been a growing appreciation of the importance of identifying and treating cognitive impairment associated with bipolar disorder (BD) since it persists in remission periods. Evidence indicates that neurocognitive dysfunction may significantly influence patients' psychosocial outcomes. An ever increasing body of research seeks to achieve a better understanding of potential moderators contributing to cognitive impairment in BD in order to develop prevention strategies and effective treatments. This review provides an overview of the available data from studies examining treatments for cognitive dysfunction in BD as well as potential novel treatments, from both pharmacological and psychological perspectives. All these data encourage the development of further studies to find effective strategies to prevent and treat cognitive impairment associated with bipolar disorder. These efforts may ultimately lead to an improvement of psychosocial functioning in these patients.

Key words: cognitive impairment, bipolar disorder, cognitive remediation, functional remediation

INTRODUCTION

The study of neurocognitive impairment, its causes and consequences, as well as the development of new therapeutic strategies to manage or even to prevent this kind of deficits, is nowadays one of the hottest areas of research in bipolar disorder (BD) (Martinez-Aran and Vieta, 2015). Data from different meta-analyses confirm that most patients with bipolar disorder show neurocognitive dysfunction, even during euthymia (Robinson et al., 2006; Bourne et al., 2013; Bortolato et al., 2015). Some of these neurocognitive deficits seem to be present not only in the early course of the illness (Torres et al., 2010; Lee et al., 2014;Bora and Pantelis, 2015) but also in premorbid stages before the illness onset (Martino et al., 2015). According to the most recent meta-analyses, the most affected domains, with effect sizes ranging from moderate to high, are attention, verbal learning and memory and executive functions, whereas premorbid intelligence appears to be preserved (Kurtz and Gerraty, 2009; (Bourne, et al., 2013). Nevertheless, it is worth mentioning that the effect sizes have become smaller since the first meta-analysis was published. Although cognitive abnormalities are present across all illness phases, they are usually more notable during acute episodes (Kurtz and Gerraty, 2009). ~~For instance, patients could present a poorer verbal learning performance during manic episodes, and bipolar depressed patients may exhibit lower performance in verbal fluency tasks.~~ Due to the fact that BD has a high heritability, it is not surprising that unaffected first-degree relatives and offspring of patients with BD present mild cognitive dysfunctions (De la Serna et al., 2016). In this sense, some authors have suggested that neurocognitive deficits could be considered as putative endophenotypes of BD (Arts et al., 2008; Balanzá-Martínez et al., 2008; Bora et al., 2009).

In the last ten years, there is also growing evidence for impairment in some social cognition domains even during periods of remission (Samamé et al., 2012, 2015). In general, evidence supports a theory of mind deficit in euthymic bipolar patients, whereas it remains unclear

whether substantial deficits in other social cognition dimensions could persist in euthymic patients with BD (Bora and Pantelis, 2016). Importantly, two points need to be kept in mind regarding social cognition: first, there is a large number of available tasks that evaluate social cognition domains with different level of complexity and quality; second, some findings point out that other neurocognitive deficits may influence social cognitive performance and this issue deserves further exploration (Samamé et al., 2012).

Evidence points out that the neurocognitive impairment profile observed in patients with BD is similar to that showed in patients with schizophrenia although in a lesser extent, therefore, differences between the two disorders seem to be predominantly quantitative rather than qualitative (Daban et al., 2006). Patients with schizophrenia also significantly underperform bipolar patients in social cognitive tasks, such as emotion recognition and theory of mind similarly to findings for other neurocognitive tasks (Bora and Pantelis, 2016). Nevertheless, an important matter is that studies comparing both psychiatric disorders have not taken into consideration the potential effect of the extant cognitive variability in both disorders. Overall, approximately 40-60% of patients with BD exhibit neurocognitive impairment, with a large heterogeneity among them. ~~as it will be discussed later. There has been disparity in the establishment of a threshold as well as criteria for the cognitive impairment in BD, with some studies being more conservative than others. Hence, percentages of cognitive impairment in the existing studies vary according to the neuropsychological tool or the cut-off used to consider impairment (i.e. 1 or 2 standard deviations below the mean).~~ Beyond the percentage of neurocognitively impaired bipolar patients, converging data from a few recent studies suggest that there are several neurocognitive subtypes among bipolar patients, which may also explain, at least in part, the extant variability in psychosocial functioning among patients. The use of cluster analysis approaches has enabled different authors to detect distinct neurocognitive profiles among both bipolar I and bipolar II patients: one with a normal performance, one (or two groups) with selective modest impairments and, lastly, another

cluster showing a more globally severe cognitive impairment (i.e., encompassing several domains) (Burdick et al., 2014; Bora et al., 2016; Jensen et al., 2016; Solé et al., 2016). It seems that several clinical (e.g. number of episodes, psychotic symptoms, etc) or sociodemographic variables (e.g. schooling, premorbid intelligence quotient, etc.) would be associated with the neurocognitive variability, although we cannot dismiss methodological issues as well as other intrinsic individual factors (e.g. motivation, self-esteem, etc.) as potential factors.

As some authors suggest, the neurocognitive variability might also reflect an etiological heterogeneity in BD including potential different subtypes associated with different genetic susceptibility factors (Bora, 2016). Evidence shows that BD shares some susceptibility genes with schizophrenia whereas some other genetic susceptibility factors seem to be specific of each disorder (Lichtenstein et al., 2009; Craddock et al., 2010). Taking all these findings into consideration, it has been hypothesized the existence of two groups: a group of bipolar patients characterized by normal neurodevelopmental and cognitive functioning, whose cognitive decline is probably influenced by the impact of repetitive affective episodes; and another much smaller group of patients presenting with a pattern of cognitive impairment comparable to that observed in schizophrenia, characterized by a low premorbid cognitive functioning before illness onset. This latter group of patients would share common genetic risk factors with schizophrenia and might be associated with neurodevelopmental abnormalities. Nonetheless, at this point, further genetic and neurobiological research is needed to confirm this hypothesis. Moreover, inconsistent findings between the extant cross-sectional and longitudinal studies highlight the necessity for further research to elucidate the veritable evolution of cognitive dysfunction in bipolar illness and potential selection bias in longitudinal studies, since disturbance progress following repeated episodes is not entirely clear. Most of cross-sectional studies find an association between cognitive impairment and number of episodes, whereas the longitudinal ones indicate a stable pattern over time (Budde et al., 2014; Samame et al., 2014). During the last decade different staging model approaches have

been proposed for BD (Berk et al., 2007; Kapczinski et al., 2008). These models assume an underlying pathophysiological process of neuroprogression associated with cognitive decline among other neurobiochemical changes, however, not every patient will proceed through all stages. Therefore, an early identification of which patients will develop a neuroprogressive disorder as well as the link with staging models are some of the challenges in the upcoming years (Rosa et al., 2014; Passos et al., 2016). .

It is also remarkable that neurocognitive deficits are not specific of BD and they may be considered as a common dimension across disparate psychiatric disorders, thus, a trans-nosological domain (Millan et al., 2015; Vieta, 2016). In this vein, the Research Domain Criteria (RDoc) is an alternative approach with the purpose of conducting research in terms of dimensions, defined by neurobiology and behavioral measures, which cut across traditional diagnostic categories. This framework incorporates genetics, neuroimaging and cognitive sciences for a new classification of mental disorders (Cuthbert, 2014), where the cognitive system is among the proposed higher order domains. Although this framework was designed to serve templates for research, interestingly it might enrich current DSM diagnoses with more individualized nuances by highlighting factors that mediate or moderate the clinical course and response to treatment. Combining this information, in a hybrid model, might provide a powerful prognostic capacity regarding the course and treatment response as well as help to guide the treatment planning (Yager et al. 2017).

It is worth mentioning that neurocognitive impairment needs to be considered a therapeutic clinical target in order to improve both psychosocial functioning and quality of life of patients with BD (Grande et al., 2016). Available evidence underscores that cognitive dysfunction is a critical mediator of adverse psychosocial outcomes in BD and a predictor of unfavorable employment outcomes (Tse et al., 2014; Baune and Malhi, 2015;). It is worthy to note that similarly to cognitive dysfunction, functional deficits persist even after symptomatic remission

in a significant subset of patients with BD, thus aggregating additional burden to patients and also possibly increasing illness-related direct and indirect costs. In this sense, BD is ranked among the leading causes of burden of disease worldwide associated with a high level of disability-adjusted life years (Catalá-López, et al., 2013). ~~Fortunately, in the last years some efforts have been done to develop interventions addressing neurocognitive function in BD. Nevertheless, this area of research is still on its early developmental stages.~~

The fact of considering cognitive dysfunction as a core feature of BD has led to a growing interest in developing both pharmacological and non-pharmacological prevention strategies to treat this type of deficits. Therefore, the overarching aim of this review is to draw a comprehensive picture of extant treatment approaches that primary address cognitive dysfunction in BD and other potential treatments, and provide some clinical recommendations for further research in this field.~~. of the complexity of cognitive dysfunction in BD, focusing on: 1) describing the magnitude of cognitive dysfunction in BD, 2) identifying potential moderators - factors that may influence cognition- that underlie cognitive impairment and 3) describing treatment approaches that primary address cognitive dysfunction in BD.~~

~~MAGNITUDE OF COGNITIVE IMPAIRMENT~~

~~This qualitative and quantitative heterogeneity of neurocognitive impairment has also observed in other psychiatric conditions such as schizophrenia (Lewandowski et al., 2014). In other studies assessing cross-diagnostic samples, patients with BD represent a larger proportion in the neuropsychologically normal group in comparison to schizophrenic patients which are more prone to be severely impaired (Lewandowski et al., 2014; Bora et al., 2016).~~

~~Differences in clinical or sociodemographic variables (e.g., schooling) might at least in part explain the variability of neurocognitive performances across studies, as will be reviewed later~~

in this article. Across the different studies using clustering methods, patients belonging to the cluster with severe neurocognitive deficits had a significantly poorer educational attainment and/or a lower premorbid intelligence quotient (IQ) (Bora et al., 2016; Solé et al., 2016). Burdick and colleagues also observed that their selectively impaired group had a higher number of total affective episodes supporting the negative impact of affective recurrences on neurocognitive (Burdick et al., 2014). Moreover, these studies also showed that the more neurocognitively impairment, the poorer the functional outcome (Jensen et al., 2016; Solé et al., 2016).

Note that the neurocognitive variability should be considered when we interpret data coming from meta-analytic and systematic-review findings. As has been mentioned before, several clinical factors might influence this heterogeneity. Nevertheless, we cannot dismiss methodological issues as well as other intrinsic individual factors (e.g. motivation, self-esteem, etc.) as potential factors explaining, at least partially, this variability.

MODERATORS OF NEUROCOGNITIVE FUNCTIONING

The study of factors involved in neurocognitive impairment is one of the first steps to prevent or mitigate the neurocognitive dysfunction associated with BD. Nevertheless, it is not well established yet whether neurocognitive deficits are due to neurodevelopmental abnormalities, to the illness progression or if they reflect part of both processes (Goodwin et al., 2008). Altogether, neurocognitive dysfunction in BD seems to be multifactorial where a series of clinical factors has been suggested to exert some effect, direct or indirectly, on neurocognitive functioning (see Table 1.).

Number of episodes and chronicity: Many of the cross-sectional studies point towards an association between number of affective episodes and neurocognitive impairment suggesting a progressive cognitive decline. When patients with multiple manic episodes were compared with patients with a first manic episode, those patients with a recurrence of manic episodes

showed more deficits in executive functions and episodic memory and reduced psychomotor speed (López-Jaramillo et al., 2010; Hellvin et al., 2012). These findings also support those studies on neuroanatomical differences in bipolar I patients. Nonetheless, we cannot fail to mention other several points. First, recurrence of depressive episodes has also been suggested to exert a detrimental effect on cognition in some study, though this association has been less replicated (Summers et al., 2006). Secondly, contrary to most cross sectional studies, evidence from longitudinal studies is not in accordance with a neurocognitive progression in BD. As a whole, the follow up studies have found a stable pattern of neurocognitive impairment over time (Budde and Schulze, 2014; Samamé et al., 2014). Nevertheless, the longer follow-up study carried so far revealed that most neurocognitive functions remained stable over time with the exception of a worsening in the executive functions, which was associated with illness duration and subclinical depressive symptoms (Torrent et al., 2012). Therefore, short time frames of assessment in most of the longitudinal studies could explain the lack of a cognitive function decline. Thirdly, data from a meta-analytic study indicate that neurocognitive impairment in first episode bipolar patients was equivalent to that observed on patients with a chronic course of the illness (Bora and Pantelis, 2015). Explanations for this apparent contradiction may involve the fact that the patients who were able to stay for long-term follow-up might not be representative of the majority of bipolar patients; they may be more adherent and may have many of the "good prognosis" indicators that protect against cognitive decline.

Another interesting study showed that cognitive impairment was present in remitted bipolar patients from the first manic episode. However, those episode free patients improved cognitively in the year following the first manic episode, so impairment seems reversible when compared to patients who experienced recurrences of affective episodes (Kozicky et al., 2014). Hence, these results would suggest the need to implement interventions in the early stages to avoid affective recurrences and to reverse neurocognitive deficits too.

Psychotic symptoms: Several studies reported an association between lifetime history of psychotic symptoms and neurocognitive impairment, mainly with a deleterious effect on executive functions and verbal memory (Glahn et al., 2007; Martinez-Aran et al., 2008). Besides, some authors suggested that neurocognitive dysfunction depends on history of psychosis rather than the diagnostic category *per se*, supporting a dimensional approach in the severe psychiatric illnesses classification systems (Simonsen et al., 2009). Nevertheless, we can also found some studies that did not found any relationship between cognitive impairment and psychotic symptomatology (Selva et al., 2007). These inconsistent findings are probably due to the use of small sample which include symptomatic patients. Overall, according to meta-analytic findings, the effect of the history of psychosis in BD is modest, not supporting a complete categorical distinction between patients with or without history of psychotic symptoms (Bora et al., 2010).

Subclinical depressive symptoms: Another important factor that may exert an impact on psychosocial outcome and also on cognition is the subclinical depressive symptomatology, even at low levels (Bonnín et al., 2011; Torrent et al., 2012). A recent study using a path analysis found that verbal memory had a significant indirect effect on functional outcome, partly mediating the relationship between depressive symptoms and functional status (Bonnín et al., 2014). Verbal memory has been linked to functional outcome in several studies and previous literature also links subclinical symptomatology with verbal memory (Martinez-Aran et al., 2007; Martino et al., 2009; Bonnín et al., 2010). Thus, depressive symptoms are not only negatively associated with functional outcome, but also affect verbal memory performance.

Diagnostic subtype of bipolar disorder: Due to the fact that the two main diagnostic subtypes of BD (bipolar I and II) present with a different clinical course and that manic and depressive episodes might exert a differential influence over cognitive function, a reduced number of studies have compared neurocognitive performance between both diagnostic subtypes.

Despite some constraints affecting findings in this area of research, the vast majority of studies comparing euthymic samples detected a worse neurocognitive performance in patients with bipolar I subtype compared to bipolar II subtype, especially in verbal and visual memory domains and some tasks related with executive functions (e.g. verbal fluency) (Bora, 2011; Solé et al., 2011). Nevertheless, differences between the two subtypes seem to be small. This little but worse performance in bipolar I patients might be more consistently related with manic episodes which seem to exert a negative long-term effect on neuropsychological performance.

Pharmacological treatment: Medication constitutes an important confounding factor which is not easy to control for due to the fact that most patients with BD are usually treated with combinations of different drugs and few patients are medication-free. In addition, medication may exert conflicting effects on cognition: although some pharmacological treatments may have an indirectly protective role reducing affective and psychotic symptomatology, several drugs may not be free of neuropsychological negative side effects, especially in complex combinations. Besides, there is some controversy regarding neurotoxic and neuroprotective effects of several agents. For instance, concerning lithium, the most widely studied mood stabilizer with regards to its neurocognitive effects, seems to has a negative, although minor, effect on verbal memory and psychomotor speed (Wingo et al., 2009). Nevertheless, some preclinical studies point out the neuroprotective and neurotrophic effects of lithium. In fact, an interesting study showed that a small sample of excellent lithium responders exhibited normal cognitive functioning and plasma BDNF (brain derived neurotrophic factor) levels compared to the remaining lithium patients where the effect of lithium was not optimal (Rybakowski and Suwalska, 2010). With regards to antipsychotic and anticepileptic treatments, few studies have been specifically conducted with bipolar patients, with most data coming from schizophrenia or patients with epilepsy. Generally, antipsychotics have been associated with executive dysfunction and lower psychomotor speed (Frangou et al., 2005; Bora et al., 2009). After reviewing the available literature concerning BD treatment, Solé & Jimenez conclude that any

atypical antipsychotic appears as better than others with regard to its cognitive profile (Solé and Jiménez, 2015). Concerning anticonvulsants in bipolar patients, they seem to exert similar cognitive effects than those described in volunteers and patients with epilepsy (Gualtieri and Johnson, 2006). Hence, lamotrigine and oxcarbazepine have more favorable cognitive profile, whereas carbamazepine, valproic acid and topiramate have the most cognitive toxicity. Benzodiazepines, another commonly prescribed drug type among bipolar patients, can interfere with memory. Lastly, most of the studies examining the effects of antidepressants on cognitive functioning come from patients suffering a major depressive disorder (Popovic et al., 2015), and a paucity of them were conducted with non-geriatric adult samples. As a whole, antidepressants seems to have beneficial effects in reducing cognitive impairment, especially with a positive effect on psychomotor speed and delayed recall, with no significant differences between different antidepressant classes (selective serotonin reuptake inhibitors –SSRIs-, serotonin and norepinephrine reuptake inhibitors –SNRIs , dopamine modulators and norepinephrine inhibitors) (Keefe et al., 2014; Rosenblat et al., 2016).

Despite potential side effects of pharmacological treatments, studies conducted with medication-free bipolar patients, or comparing patients with or without pharmacological treatment, indicate that cognitive impairment is caused by the illness impact and little effects are due to the medication *per se* (Goswami et al., 2009).

Comorbidity: BD is often accompanied by multiple medical comorbidities. Many of these conditions could constitute additional factors that influence neurocognitive performance in bipolar patients (e.g. substances use disorder, anxiety, attention deficit hyperactivity disorder –ADHD-, etc.) (Balanzá-Martínez et al., 2010).

Wu et al. found out that bipolar II patients with a comorbid anxiety disorder showed poorer cognitive performance that those without, especially in verbal and non-verbal memory, psychomotor speed and working memory (Wu et al., 2011). Volkert and colleagues also found

that comorbid anxiety was significantly more prevalent among patients with cognitive impairment (Volkert et al., 2015). Furthermore, Levy and colleagues also found more symptoms of acute anxiety (a higher arousal) during neuropsychological tasks in those euthymic bipolar patients showing a poorer performance than in the healthy control group (Levy, 2013). This group of authors suggested that symptoms of acute anxiety triggered by cognitive challenge may compromise cognitive functioning in patients with BD.

Substance abuse is also particularly common. Bipolar patients with comorbid alcohol abuse exhibited more executive dysfunction and verbal and visual memory deficits than those without comorbidity (van Gorp et al., 1998; Levy et al., 2008). Even bipolar patients with previous history of alcohol consumption exhibit a poorer performance in inhibitory control in comparison with healthy controls (Sanchez-Moreno et al., 2009), however, no other differences were detected when compared to patients without history of consumption. Maybe, the potential negative effects of alcohol could be reversible after a long timeframe of abstinence. Nonetheless, comorbid patients had a less favorable period of recovery of cognitive deficits over the course of mood remission after suffering an affective episode than those bipolar patients without comorbidity (Levy et al., 2013).

Alcohol abusers also showed higher impulsivity in all the components of the Barratt Impulsiveness Scale (i.e. non-planning, attentional and motor) when compared with non-comorbid bipolar patients (Nery et al., 2013). In this line, another study showed that performance in the Iowa Gambling Test (IGT) is a good predictor of risk for future drug use in bipolar patients with stimulant dependence (Nejtek et al., 2013).

Concerning ADHD, the first study including a comorbid BD+ADHD group showed that this group of patients performed significantly worse that both a pure ADHD and a healthy control group (Silva et al., 2014). Therefore, according to these results, authors suggested that some executive dysfunction, such as set-shifting deficits, in comorbid ADHD+BD patients may to a

large extent be attributable to comorbid BD. Nevertheless this study was only focused on executive functions and was also lacking of a pure bipolar patients group. Recently, Torres and colleagues compared four groups (euthymic bipolar patients, ADHD patients, comorbid BD+ADHD patients and a healthy control group) for the first time (I. Torres, unpublished observations). This study detected that the comorbid group had a similar neurocognitive profile than pure bipolar patients, most likely reflecting the same neurobiological basis. The group of ADHD patients exhibited more selective cognitive impairment limited to memory and attention domains, although those ADHD patients without pharmacological treatment had a similar cognitive profile to bipolar patients. Therefore, these results also suggest that cognitive profile in adult comorbid ADHD+BD seems to be more related to BD than to ADHD.

Overweight and obesity are other highly prevalent comorbidity among bipolar patients with studies reporting a negative impact on the course of the illness, with an increasing risk of developing diseases associated with obesity (e.g. diabetes mellitus, hypertension, etc.) (Liu et al., 2013). Overweight produces several pathophysiological changes (cardiovascular diseases, insulin regulation, inflammation, etc.) affecting brain regions that may impact on neurocognitive function. Some studies showed that those euthymic bipolar patients with overweight/obesity have a poorer neurocognitive execution than those without, especially in verbal learning and memory domain (Yim et al., 2012; Depp et al., 2014; Lackner et al., 2015). Probably both conditions (BD and overweight) contribute to neurocognitive impairment in independent ways, however, the combination of both entails higher neurocognitive deficits.

Recognizing comorbidities is an important issue since some of them may complicate not only the course and treatment of patients but also may contribute to the magnitude of cognitive dysfunction adding other potential pathophysiological routes. But more important is the fact that treating some of these conditions may ameliorate cognitive impairment since some of them may be modifiable.

~~***Childhood adversity:*** Adverse life events, as childhood abuse or neglect, are frequent in bipolar patients and have been related to worsening the clinical course of the illness (Daruy-Filho et al., 2011). Besides that, several studies indicate that traumatic events during childhood are associated with structural and functional brain alterations (Quidé et al., 2016). Savitz and colleagues found an association between sexual abuse, emotional abuse and neglect with poorer performance on measures of verbal/visual memory and executive functions in patients with BD (Savitz et al., 2008). Marshall and co-workers also found a significant main effect of trauma in inhibitory control accuracy not only in bipolar patients but also in healthy individuals (Marshall et al., 2016). In the same vein, Russo found that stable bipolar patients with a childhood history of emotional neglect performed worse in recognizing anger in tasks of facial emotion recognition than those without such a history (Russo et al., 2015). These authors speculated that the fact of suffering childhood maltreatment might lead to an increased vulnerability to develop more severe emotional dysregulation through abnormal neurodevelopment and consequently impaired emotional processing. Bücker and colleagues also detected an early influence of childhood trauma on cognition early in the course of the illness, after the first manic episode, showing a more severe cognitive impairment in those patients with history of childhood trauma (Bücker et al., 2013). This same group of authors identified a significant reduction in total and regional volumes of the corpus callosum in a sample of bipolar patients with trauma recently recovered of a first manic episode compared with those without trauma (Bücker et al., 2014). Interestingly, another group of authors found that, although level of history of childhood trauma was higher in a group of schizophrenic patients, childhood trauma was more associated with poorer cognitive performance in the sample of first-episode affective psychoses (bipolar and psychotic depression) than in the non-affective psychoses (Aas et al., 2011). Lastly, a recent study examined the potential impact of childhood trauma specifically on distinct neurocognitive profiles using a data-driven analysis (E. Jimenez, personal communication). Higher levels of childhood trauma assessed with the~~

Childhood Trauma Questionnaire (CTQ) were detected in those patients clustered in the low performance group. Moreover, the total CTQ score and the estimated IQ significantly contributed to differentiate among the different neurocognitive subgroups. Interestingly, this study found that physical negligence, which has been traditionally underreported, may also impact cognitive performance. Therefore, it should be necessary to assess and target mild forms of maltreatment too.

Despite the significant impact that may exert early life stress and maltreatment in bipolar patients, and particularly in cognitive functioning, there are few studies investigating its effects and it constitutes a crucial issue that awaits future research with longitudinal studies.

***Cognitive reserve*:** Cognitive reserve reflects the capacity of the adult brain to endure neuropathology, minimizing clinical manifestations and allowing a successful accomplishment of cognitive tasks (Stern, 2009). This concept, commonly used in neurology, has also been applied in neuropsychiatric disorders during the last years. Genetic and neurodevelopmental factors determine cognitive reserve, however, exposure to specific environmental factors as education, lifestyle, mental and physical activities may also influence it. There are different, being The most commonly proxy indicators of cognitive reserve used are years of educational attainment, leisure activities and premorbid IQ.

Very recently some studies have suggested that cognitive reserve may be a significant predictor of both cognitive and psychosocial outcome in euthymic bipolar patients which indicates that individual differences of brain characteristics and usage before illness onset may influence the future functional and neuropsychological outcome (Anaya et al., 2015; Forcada et al., 2015). Interestingly, a higher cognitive reserve has also been demonstrated to be associated with better neurocognitive, functional and clinical outcomes in first psychotic episodes and to be predictive of functioning at two-year follow-up of this group of patients (Amoretti et al., 2016). Altogether, these data suggested that early interventions to enrich

~~cognitive reserve might result in minimizing the detrimental neuropsychological and functional impact caused by the illness (Vieta, 2015).~~

~~Cognitive reserve is still a new concept in the BD field, therefore, further research is guaranteed in the next years to have a better understanding of individual differences.~~

~~Other potential confounders that might be also influencing cognition have been less studied as rapid cycling (Wu et al., 2016), affective temperaments (Russo et al., 2014) or history of obstetric complications (Martino et al., 2008) and all of them deserve further research.~~

TREATMENT AND PREVENTION STRATEGIES

Pharmacotherapy

From a pharmacologically therapeutic perspective, different drugs with potential beneficial effects for the treatment of neurocognitive impairment have been examined (e.g. some cholinesterase inhibitors, glutamate receptor antagonists, glucocorticoid receptor antagonists, dopaminergic agonists, intranasal insulin, some antioxidants, erythropoietin, etc.). Unfortunately, there is no well-established pharmacological treatment for cognitive impairment since studies have yielded mixed results with no convincing effects.

Among all the components tested, very few of them have demonstrated positive effects on cognition. Mifepristone, a corticosteroid receptor antagonist, showed preliminary evidence to improve spatial working memory in depressed bipolar patients in two studies, the enhancement occurring in the absence of an improvement in depressed mood (Young et al., 2004; Watson et al. 2012). Pramipexole, a dopaminergic agonist, could have a beneficial effect on processing speed and working memory, but it was only observed in those euthymic bipolar I patients in a post-hoc analyses of a 8-week, double-blind, placebo-controlled trial (Burdick et

al., 2012). Another agent that showed an improvement in a secondary measure of executive function (the trail making test part-B) in euthymic patients was the intranasal insulin. However, this component did not show any therapeutic effect on the primary cognition outcomes neither on other secondary cognitive outcomes (memory measures) (McIntyre et al., 2012). Another compound demonstrating a positive effect in some cognitive measures in euthymic or subsyndromal bipolar patients was the extract of *Withania somnifera,* an herbal medicine with antioxidant and neuroprotective effects (Chengappa et al., 2013). Patients taking this agent showed a better performance mainly in measures related to auditory-verbal working memory. Erythropoietin (EPO) was another adjunctive treatment that improved some secondary and tertiary cognitive measures related to sustained attention, working memory, executive function and recognition of facial expression in euthymic patients, but not in verbal memory which was the primary outcome (Miskowiak et al., 2014). Despite the negative primary outcome on this study, positive effects on secondary outcomes are encouraging, so it warrants the investigation with non-hematopoietic erythropoietin analogs since its hematopoietic activity limits its clinical use. Galantamine, a cholinesterase inhibitor, has been proved in more studies. Although some of them have reported a potential benefit in verbal memory, even for those patients receiving electroconvulsive therapy, these studies have important caveats and merits further investigation (Ghaemi et al., 2009; Iosifescu et al., 2009; Matthews et al., 2008; Matthews et al., 2013). Results from a large randomized, double blind controlled trial showed that N-acetyl cysteine (NAC) as an add-on treatment in patients with BD failed to find benefits in cognitive functioning (Berk et al., 2008; Berk et al., 2012; Dean et al., 2012). Instead, when patients with psychotic BD from this previous study were grouped with other patients with schizophrenia and were analyzed as a whole of patients with psychotic features, those subjects following a treatment with NAC during 6 months enhanced their working memory performance (Rapado-Castro et al., 2016). Therefore, these results warrant an avenue for further exploration with NAC as an agent to treat cognitive dysfunction. Lastly, given the

preliminary support for cognitive enhancement of lurasidone in patients with schizophrenia, a randomized, open-label pilot trial has examined the efficacy of this agent as an add-on treatment in comparison with treatment as usual (TAU) in euthymic bipolar I patients (Yatham et al., 2017). There was a greater improvement for the primary outcome (changes in a global cognition score) in the lurasidone group compared with the TAU group. It was also observed an improvement in specific cognitive measures related to visual memory and working memory as well as in subjective cognitive complaints. Although the exact mechanisms underlying the cognitive effects of lurasidone are still unclear, its high affinity for 5-HT_7 receptors might be an important contributor.

There is a series of other investigated compounds with, at least for now, negative results on cognition, as methylene blue (Alda et al., 2017) or with only improvement in subjective cognition such as donepezil, therefore, with a lower evidence of effect on cognitive performance (Gildengers et al., 2008). Methylene blue, as and adjunctive treatment with lamotrigine, seems not to have significant effects on cognition, whereas patients on it significantly improved residual symptoms of depression (Alda et al., 2017).

Among all the studies on pharmacological treatments, 11 out of 14 were randomized controlled trials conducted only with patients with BD and 3 of them were open label studies. Miskowiak and colleagues point out that most of the cited studies with positive results have a significant risk of bias related to details of the randomization process and the lack of test cognition as a primary outcomes (for a broader information and a systematic review see Sanches et al., 2015 and Miskowiak et al., 2016).

Notwithstanding the efforts done so far, no drug has been approved as a pro-cognitive enhancer for BD, although some of these drugs appear as promising candidates. Therefore, further research is required to find compounds which may became considered as reliably efficacious pro-cognitive enhancers. Meanwhile, clinicians should bear in mind a rational use

of drugs to treat the illness, as well as the cognitive profile of each compound in order to minimize the cognitive side-effects for each individual. In this sense, medication may exert conflicting effects on cognition; while some pharmacological treatments may have an indirectly protective role reducing affective and psychotic symptomatology, several drugs may not be free of neuropsychological negative side effects, especially in complex combinations. Besides, there is some controversy regarding neurotoxic and neuroprotective effects of several agents, as lithium (Wingo et al., 2009). In fact, an interesting study showed that a small sample of excellent lithium responders exhibited normal cognitive functioning and plasma BDNF (brain derived neurotrophic factor) levels compared to the remaining lithium patients where the effect of lithium was not optimal (Rybakowski and Suwalska, 2010). After reviewing the available literature concerning BD treatment, Solé & Jimenez concluded that none specific atypical antipsychotic appears as better than the others with regard to its cognitive profile (Solé and Jiménez, 2015). Concerning anticonvulsants in bipolar patients, they seem to exert similar cognitive effects than those described in volunteers and patients with epilepsy (Gualtieri and Johnson, 2006). Lastly, as a whole, antidepressants seems to have beneficial effects in reducing cognitive impairment, especially with a positive effect on psychomotor speed and delayed recall, with no significant differences between different antidepressant classes (Keefe et al., 2014; Rosenblat et al., 2016). Despite the potential side effects of pharmacological treatments, studies conducted with medication-free bipolar patients, indicate that cognitive impairment is caused by the illness impact and little effects are due to the medication *per se* (Goswami et al., 2009).

Non-pharmacological approaches

Prior research on *cognitive remediation* in schizophrenia has provided some guides for BD. Nevertheless, as abovementioned, neurocognitive dysfunction in schizophrenia is of greater magnitude than the kind of deficits observed in patients with BD. Therefore, it is necessary to

adjust or to develop new interventions specifically addressed to the characteristics of the latter group~~. Some authors have suggested some recommendations for developing specific cognitive remediation programs for bipolar illness~~ (see Fuentes-Durá et al., 2012).

Very few studies have focused only on bipolar patients, and most of them were conducted with mixed affective disorder samples and were not rigorously controlled. Regarding cognitive or functional remediation, there are 2 open label studies and 2 randomized controlled trials. The first study, focused specifically on bipolar patients, was a small open trial for subjects with residual depressive symptoms (Deckersbach et al., 2010). This study detected a reduction of depressive symptoms and an increase in psychosocial functioning in patients after receiving 14 individual sessions of cognitive remediation. Therefore the promising results of this study paved the way towards more studies on cognitive rehabilitation in bipolar disorder.

Functional remediation is an innovative intervention aimed at restoring psychosocial functioning specifically designed for bipolar patients. In 21 weekly sessions functional remediation provides several neurocognitive strategies and techniques for daily life to tackle the main neurocognitive deficits associated with BD (e.g. attention, memory, and executive functions). ~~The first block of this intervention consists of a group of psychoeducative sessions about neurocognition and the impact of neurocognitive impairment in their daily lives, trying to increase, in this way, the insight about neurocognitive dysfunction. Family is involved in this process in order to increase the awareness of neurocognitive impairment associated with bipolar illness and to encourage the practice of all the learned strategies in each session and the reinforcement. The following three blocks are devoted to manage the three main affected cognitive areas related to the disorder, aforementioned. Then, the last block addresses some communication skills and techniques to the stress management in order to promote the autonomy of patients.~~ The intervention includes both individual and group format tasks in an ecologic setting in order to establish a connection between the learned skills and strategies

with daily life situations of patients (as work, autonomy, etc.). The efficacy of functional remediation was proven in a randomized controlled trial comparing functional remediation to psychoeducation and to TAU (Torrent et al., 2013). Patients receiving the functional remediation program improved the overall psychosocial outcome and, specifically, the interpersonal and occupational functioning. The intervention was also effective in bipolar II patients (Solé et al., 2015). Secondary analysis showed that the intervention also improved neurocognitive outcomes in the subsample of cognitively impaired patients (Bonnin et al., 2015). Even more importantly, the functional improvement in the functional remediation group persisted at 1-year follow-up compared with the other two treatment groups when the whole sample was considered (Bonnin et al., 2016). Autonomy was the functional domain that improved at 1-year follow-up and, interestingly, verbal memory also significantly improved from baseline to endpoint ~~1-year follow-up~~, an improvement that had not been detected just after finishing the intervention. Functional remediation also seems to be effective in patients with subsyndromal symptomatology (Sanchez-Moreno et al., 2017).

More recently, a small open pilot study assessing the feasibility of a briefer functional remediation program, which combined individual and group sessions, also showed a positive effect on overall psychosocial functioning in a sample of bipolar I patients (Zyto et al., 2016). This type of format seems to allow a more tailored approach to facilitate achieving personal goals.

In contrast, in another randomized controlled trial conducted by Demant and colleagues, cognitive remediation was not effective to ameliorate cognitive dysfunction in partial remitted bipolar patients with a 12 weeks group-based program (Demant et al., 2015). As the authors suggested, a more intensive and durable intervention may be necessary to improve cognition in bipolar patients.

Due to the fast advance in information and communication technology (ICT) issues, one challenge in cognitive remediation is to implement computerized neurocognitive treatments in an effective manner. This kind of intervention delivery makes easier the accessibility to patients engaged in working life as well as to younger users who are familiar with new technologies. In fact, the aforementioned study by Demant and colleagues introduced a computer-assisted cognitive training as a part of the cognitive remediation program. Concerning this topic, Lewandowski and colleagues have published a study protocol for assessing the efficacy of an internet-based cognitive remediation program for patients with BD type I (Lewandowski et al., 2016), similarly to Strawbridge and co-workers (Strawbridge et al., 2016). -Unfortunately, results of both studies -are not available yet.

Due to the fact that social cognition also seems to be involved in psychosocial functioning, an interest in developing strategies to enhance social cognition has emerged over the last years (Lahera et al., 2012). Nevertheless, any study has been exclusively focused on bipolar patients. Lahera and co-workers assessed the efficacy of the Social Cognition and Interaction Training (SCIT), an intervention originally developed for patients with schizophrenia, in a sample mostly composed by bipolar patients but also some schizoaffective patients (Lahera et al., 2013). The intervention, addressed to improve emotion perception, attributional style and theory of mind, was found to be effective improving these social cognition domains but not social functioning. Maybe, interventions aimed to train social cognition would need to be adapted to the specific profile of social cognitive deficits observed in BD. In any case, an extension of social cognition training in cognitive/functional remediation interventions would be an interesting option of research for bipolar patients.

In the last decade there has been a growing interest in implementing mindfulness-based interventions for the treatment of mental disorders, with some studies focusing on bipolar disorder. Overall, mindfulness appears as a useful intervention for the reduction of anxiety

symptoms and, probably, to reduce depressed symptoms (Reinares et al., 2014). More recently, some studies have analyzed the impact of mindfulness on cognitive functioning in BD. For example, the study of Stange and colleagues provides preliminary results that mindfulness may be an adjunct treatment option to medication to improve cognitive functioning in BD (Stange et al., 2011). Likewise, the cognitive remediation program proposed by Demant and colleagues also included some mindfulness exercises to practice at home and at the beginning of each session, as a mean to enhance the attentional capacity (Demant et al., 2015). Nevertheless, further research is needed in this area.

Therefore, as noted, interventions focused on the enhancement of cognition and psychosocial functioning in bipolar patients are still in its early stages and further research is needed in order to find the key components of cognitive and/or functional remediation.

~~Several positive effects have been associated with *physical exercise* such as increased production of brain neurotrophic factors and increased activity of specific neurotransmitters. The results obtained across other psychiatric or neurological conditions, as well as on aging, suggest that aerobic physical exercise may also have unequivocal beneficial effects on cognitive functioning in BD, though no studies are available in this population (Kucyi et al., 2010; Malchow et al., 2013). Most of the studies about the effects of exercise in affective disorders, which are generally conducted with patients with major depressive disorder, are focused on mood, anxiety and quality of life. A reduction in these affective symptoms might lead to neurocognitive changes or target a common pathophysiology underlying both affective and neurocognitive mechanisms.~~

Lastly, some evidence grows concerning the role of *non-invasive brain stimulation techniques*, such as the transcranial magnetic stimulation (TMS), in the management of neurocognitive impairment in some neurological conditions. These interventions seem to modulate

neuroplasticity processes. Deep transcranial magnetic stimulation (DTMS) is a novel alternative to repetitive TMS which has been associated with small short-term improvement in sustained attention and larger improvement in spatial and visuospatial memory in unipolar depression (Minichino et al., 2012). Concerning BD, in a small open study Harel et al. detected a beneficial effect on working memory and psychomotor speed in a group of depressed bipolar patients after receiving 20 sessions of high-frequency DTMS when compared to healthy participants (Harel et al., 2011). Even so, DTMS in this group of patients also showed short-term antidepressant and anxiolytic effects, so it is difficult to conclude about the possible positive effect of DTMS on cognitive performance. Concerning the use of transcranial direct current stimulation (tDCS), on the one hand, repetitive sessions of tDCS in a group of euthymic bipolar patients provided preliminary results that concomitant prefrontal excitatory and cerebellar-inhibitory tDCS might have a positive effect on visuoespatial memory (Minichino et al., 2015). Nevertheless, this study had significant limitations as a lack of a sham control group and a limited neuropsychological assessment. On the other hand, an intra-individual cross-over study failed in proving the efficacy of a single session of tDCS improving working memory and attention in euthymic bipolar patients (Martin et al., 2015). These last results would be in contrast to those reported in other studies conducted with healthy participants. Therefore, studies with brain stimulation techniques are still rare in BD and more studies will be required to assess the magnitude of effects compared to placebo and the durability of them. Even so, these extant studies raise several methodological considerations to keep in mind for further studies in order to achieve a potential cognitive enhancement.

~~As has been mentioned previously, due to the fact that cognitive reserve may contribute to functional and cognitive outcome, it has also been suggested that the implementation of intervention that allow the modification of CR in early stages of the illness might appear as a new target in bipolar patients in order to prevent a progressive impairment (Forcada et al., 2015).~~

Other approaches to prevent cognitive impairment

While research in all these abovementioned areas proceeds, it is also be important that clinicians prevent neurocognitive impairment through different strategies. The study of factors that may moderate or mediate neurocognitive impairment is one of the first steps to prevent or mitigate the neurocognitive dysfunction associated with BD. It is not well established yet whether neurocognitive deficits are due to neurodevelopmental abnormalities, to the illness progression or if they reflect part of both processes (Goodwin et al., 2008). Altogether, neurocognitive dysfunction in BD seems to be multifactorial where a series of clinical factors has been suggested to exert some effect, direct or indirectly, on neurocognitive functioning (see Table 1.). For instance, despite evidence on longitudinal studies is not totally in accordance with a neurocognitive progression in BD, as has been mentioned before, many of the cross-sectional studies point towards an association between number of affective episodes and neurocognitive impairment, suggesting a progressive cognitive decline, especially with the recurrence of manic episodes (López-Jaramillo et al., 2010; Hellvin et al., 2012). This cognitive impairment seems to be present from the first manic episode, although episode-free patients could improve cognitively in the year following the first manic episode (Kozicky et al., 2014). Hence, these results would suggest the need to implement interventions in the early stages to avoid affective recurrences and to reverse neurocognitive deficits too. After achieving the remission of an acute episode it will be necessary to use an effective pharmacotherapy for relapse prevention, implement psychoeducation programs to avoid multiple episodes, and promote healthy habits (Sanchez-Moreno et al., 2017). Another step towards mitigating cognitive impairment will be via the treatment of those subclinical symptoms that may also impact cognitive function and psychosocial outcome, even at low levels (Bonnin et al., 2011~~; Torrent et al., 2012~~). BD is often accompanied by multiple medical comorbidities, so

recognizing them is an important issue since some of them may complicate not only the course and treatment of patients but also may contribute to the magnitude of cognitive dysfunction adding other potential pathophysiological routes. Some conditions that have been studied and could constitute additional factors influencing neurocognitive performance are substance use disorders, anxiety, the attention deficit hyperactivity disorder –ADHD- and overweight or obesity (Balanzá-Martínez et al., 2010; Yim et al., 2012; Depp et al., 2014; Lackner et al., 2015; Volkert et al., 2015; Sanchez-Moreno et al., 2009, van Gorp et al., 1998; Levy et al., 2008; Silva et al., 2014; I. Torres, unpublished observations). Importantly, treating some of these conditions may ameliorate cognitive impairment since some of them may be modifiable (see Table 2.).

Secondly, several positive effects have been associated with *physical exercise* such as increased production of brain neurotrophic factors and increased activity of specific neurotransmitters. The results obtained across other psychiatric or neurological conditions, as well as on aging, suggest that aerobic physical exercise may also have unequivocal beneficial effects on cognitive functioning in BD, though no studies are available in this population (Kucyi et al., 2010; Malchow et al., 2013). Most of the studies about the effects of exercise in affective disorders, which are generally conducted with patients with major depressive disorder, are focused on mood, anxiety and quality of life. A reduction in these affective symptoms might lead to neurocognitive changes or target a common pathophysiology underlying both affective and neurocognitive mechanisms.

A new concept commonly used in neurology, the cognitive reserve, has also been applied in neuropsychiatric disorders during the last five years. Cognitive reserve reflects the capacity of the adult brain to endure neuropathology, minimizing clinical manifestations and allowing a successful accomplishment of cognitive tasks (Stern, 2009). Genetic and neurodevelopmental factors determine cognitive reserve, however, exposure to specific environmental factors as

education, lifestyle, mental and physical activities may also influence it. The most commonly proxy indicators of cognitive reserve used are years of educational attainment, leisure activities and premorbid IQ. Very recently some studies have suggested that cognitive reserve may be a significant predictor of both cognitive and psychosocial outcome in euthymic bipolar patients, indicating that individual differences of brain characteristics and usage before illness onset may influence the future functional and neuropsychological outcome (Anaya et al., 2015; Forcada et al., 2015; Grande et al., 2016). Interestingly, a higher cognitive reserve has also been demonstrated to be associated with better neurocognitive, functional and clinical outcomes in first psychotic episodes and to be predictive of functioning at two-year follow-up of this group of patients (Amoretti et al., 2016). Altogether, these data suggest that interventions to enrich cognitive reserve in early stages of the illness might result in minimizing the detrimental neuropsychological and functional impact caused by the illness (Vieta, 2015). Even though, cognitive reserve is still a new concept in the BD field, therefore, further research is guaranteed in the next years to have a better understanding of individual differences.

FUTURE CLINICAL DIRECTIONS ~~PROSPECTS~~

Treating cognitive impairment in BD has become an important issue in the management of the patients, since it is a critical factor in psychosocial disability and lower quality of life for patients suffering from this illness (Fountoulakis et al., 2016). The presence of these deficits in early stages of the disorder also indicates that cognitive dysfunction is a target for an early identification and intervention. Therefore, it is important to better elucidate the determinants of cognitive impairment which await further research in other possible factors influencing cognition. Nevertheless, not all the bipolar patients suffer from cognitive dysfunction, therefore research on cognitive heterogeneity is an important issue to explore in order to obtain more valid and homogeneous neurocognitive phenotypes and a better understanding of those factors that may influence cognition and contribute to its variability. The study of

variability in non-chronic samples assessed in early stages (for instance, at first episodes or even at high-risk populations) is needed to establish prevention strategies and to avoid a possible progression decline. Likewise, it is also necessary to study the longitudinal trajectories of the different neurocognitive subgroups. The characterization of neurocognitive profiles may also facilitate the emergence of genetic and neurobiological studies to delineate more valid subtypes of BD. Moreover, all these kind of studies may lead to a better definition of subgroups and would provide with helpful guidance for developing more effective pharmacological or psychotherapeutic interventions contributing to enhance the management of the illness. ~~A narrowly characterization of subtypes may also allow a better identification of key factors responsible for therapeutic response to treatments.~~

Despite the increase of research investigating new pharmacological and non-pharmacological treatments over the past decade, no robust evidence of therapeutic interventions targeting cognitive deficits is currently available, due to insufficient data, and further research is needed to be largely explored and draw firm conclusions. With regards to pharmacotherapy, lurasidone, vortioxetine, omega-3-fatty acids, modafinil, vitamin-D, aspirine, and several other compounds are currently under investigation in BD. For instance, modafinil is an effective augmentation strategy for acute depressive episodes (Goss et al., 2013). A recent proof-of-concept study also showed that a single-dose modafinil could improve performance on episodic memory and working memory tasks in remitted depressed patients (Kasser et al., 2017). This agent has also given positive results not only in healthy subjects but also in cognitively high-functioning subjects as chess players (Franke et al., 2017). However, its potential beneficial effects still remains unclear in schizophrenia, with discrepant results (Bobo et al., 2011.) Taken into account all these data, some authors have hypothesized that specific subgroups of patients may benefit in cognitive performance from adjunctive modafinil, this is the case in those patients who have greater executive dysfunction or those treated with certain drugs. Therefore, a narrowly characterization of subtypes, as we have mentioned

before, may also allow a better identification of key factors responsible for therapeutic response to treatments.

Currently, a new interesting area of research, which is still in its infancy, is the pathophysiological role of the gastrointestinal system alteration in neuropsychiatric disorders. The gut microbiota also seems to influence cognition. A better knowledge of its role in bipolar disorder as well as a progress of preventive and/or therapeutic perspectives for the modulation of gut microbiota is also warranted (Salagre et al., 2017). Therapeutic strategies for altering the gut microbiome include changes in diet, probiotics, and prebiotics. In this line, probiotics are being tested as procognitive agents in other psychiatric conditions given their anti-inflammatory properties (Slyepchenko et al., 2017), so they appear as a new potential treatment to examine in bipolar illness.

Concerning cognitive remediation, there is still a lack of clinical trials for BD, with opposite findings and different approaches. Fortunately, some ongoing trials will provide more information about the benefits of cognitive remediation in the upcoming years, helping to identify the key components that might maximize the effectiveness of cognitive remediation programs (e.g. number and frequency of sessions, goals of treatment, etc.). Meanwhile, functional remediation appears as a good option to ameliorate psychosocial outcome in bipolar patients, with an effect that seems to remain in a long-term . The combination of potential pro-cognitive drugs with cognitive/functional remediation is another via to be explored in bipolar patients since the combination of both may produce more robust efficacy with cognitive enhancers increasing the physiological mechanisms through which cognitive/functional remediation produce its therapeutics effects. In this line, there is a published protocol study about a randomized controlled trial to examine the utility of combining cognitive remediation and d-cycloserine (an NMDA receptor partial agonist) in

individuals with BD (Breitborde et al., 2014). Unfortunately, results have not been published yet.

Taking into account the scarcity of adequately powered randomized trials and discrepant results on research in this field, it will be highly recommendable to conduct further studies investigating treatments targeting cognition in bipolar patients following the CONSORT (Consolidated Standards for Reporting Trials) (Moher et al., 2010) guidelines for randomized controlled trials, as Miskowiak and colleagues suggested (Miskowiak et al., 2016). Burdick and colleagues also proposed some recommendations for handling important methodological challenges associated to the complexity of the disorder in designing trials to address cognition (Burdick et al., 2015). It is mandatory to establish a consensus concerning some guidelines to implement randomized controlled trials, specifying which neurocognitive battery is optimal to screen for cognitive impairment, establishing eligibility criteria to use for the cognitive profile and mood state of participants and agreeing primary and secondary outcomes for testing treatment efficacy. Key issues for forthcoming trials include to overcome pseudospecificity by enrolling patients who are in remission from the symptomatic standpoint, to enrich the sample for cognitively impaired patients using objective screening measures, and giving preference to adjunctive designs given that most patients in remission will be taking medication at study entry.

Ultimately, novel neuromodulatory techniques also deserve further research to be considered potential treatments to mitigate cognitive deficits in patients with BD. In addition, other areas to explore are the physical exercise and potentiation of cognitive reserve to prevent the impact of cognitive dysfunction on functioning. Therefore, notwithstanding the great efforts done in the last decade to find treatments to treat neurocognitive dysfunction associated to BD, current evidence is insufficient and additional studies are required to prevent neurocognitive impairment and the associated disability.

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Table 1. Moderators of cognitive deficits in bipolar disorder (BD)
Educational attainment and premorbid Intelligence quotient (proxy variables of cognitive reserve)
Clinical symptomatology (remission vs. acute episode)
Subclinical depressive symptoms
Psychotic symptoms
Bipolar diagnostic subtype
Psychiatric or medical comorbidity
Illness duration (chronicity)
Number of episodes
Pharmacological treatment
Childhood adversity

Table 2. Potential prevention strategies in cognitive dysfunction in bipolar disorder (BD)
Prevention of multiple episodes with an effective pharmacotherapy and implementation of psychoeducation programs
Avoid concomitant medications that interfere with cognitive function
Treat subclinical depressive symptoms
Control comorbidity (mental and psychiatric)
Implement Cognitive or Functional remediation
Promote healthy habits
Aerobic physical exercise
Prescribe adjunctive pro-cognitive treatment
Use of noninvasive brain stimulation techniques (TMS, DTMS, tDCS)

Table 2. TMS= Transcranial magnetic stimulation; DTMS= Deep transcranial magnetic stimulation; tDCS= Transcranial direct current stimulation.

Figure legends

Figure 1: **neuroprogression of bipolar disorder and strategies to prevent or to treat cognitive dysfunction.**

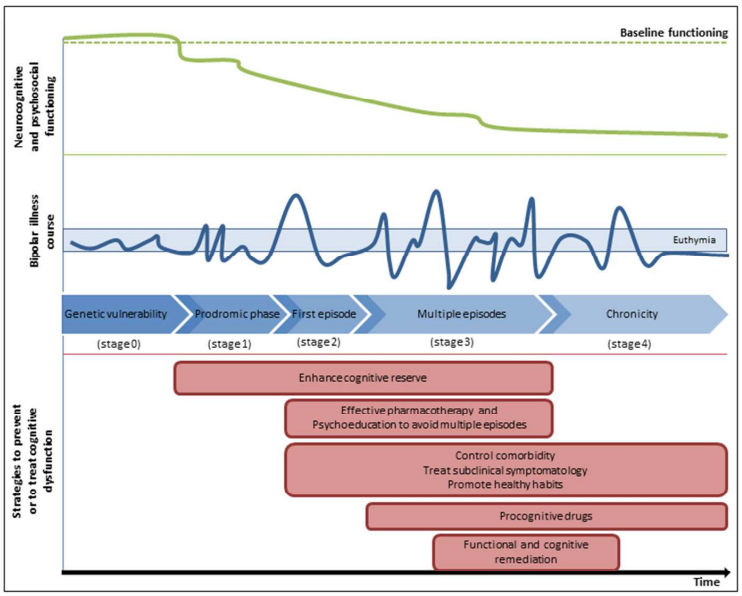

Figure 1**: neuroprogression of bipolar disorder and strategies for cognitive functioning.**

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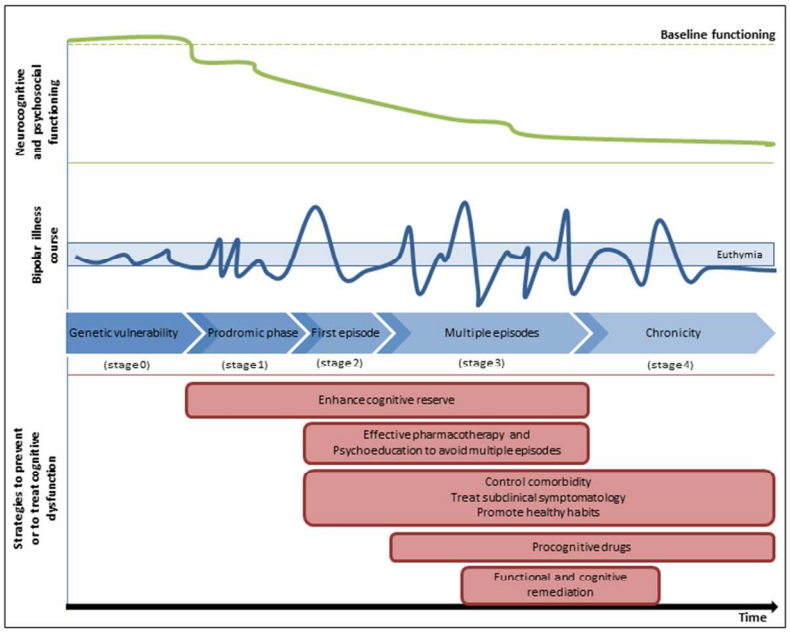

***Figure 1*: neuroprogression of bipolar disorder and strategies for cognitive functioning.**

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