REVIEW

Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies

Brisa Solé, PhD; Esther Jiménez, PhD; Carla Torrent, PhD; Maria Reinares, PhD; Caterina del Mar Bonnin, PhD; Imma Torres, PsyD; Cristina Varo, PsyD; Iria Grande, MD, PhD; Elia Valls, PsyD; Estela Salagre, MD; Jose Sanchez-Moreno, PsyD; Anabel Martinez-Aran, PhD; André F. Carvalho, MD, PhD; Eduard Vieta, MD, PhD

Barcelona Bipolar Disorders Program, Institute of Neurosciences, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain (Drs Sole, Jimenez, Torrent, Reinares, del Mar Bonnin, Torres, Varo, Grande, Valls, Salagre, Sanchez-Moreno, Martinez-Aran, and Vieta); Translational Psychiatry Research Group, Faculty of Medicine, Federal University of Ceará, Fortaleza, CE, Brazil (Dr Carvalho).

Correspondence: Eduard Vieta, MD, PhD, Hospital Clinic, 170 Villarroel St, 08036 Barcelona, Spain (evieta@clinic.ub.es).

Abstract

Over the last decade, there has been a growing appreciation of the importance of identifying and treating cognitive impairment associated with bipolar disorder, 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 bipolar disorder 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 bipolar disorder 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.

Keywords: 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 prevent these kinds of deficits is currently 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 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). Because 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 10 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, 2 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 levels 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 shown 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% to 60% of patients with BD exhibit neurocognitive impairment, with a large heterogeneity among them. 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, the existence of 2 groups has been hypothesized: 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 with 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 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; Samamé 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 Malli, 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).

The fact of considering cognitive dysfunction as a core feature of BD has led to a growing interest in developing both pharmacological and nonpharmacological prevention strategies to treat these types of deficits. Therefore, the overarching aim of
this review is to draw a comprehensive picture of extant treatment approaches that primarily address cognitive dysfunction in BD and other potential treatments and provide some clinical recommendations for further research in this field.

**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 2 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 posthoc analysis of an 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 neither on the primary cognition outcomes nor 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 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 nonhematopoietic 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 merit further investigation (Matthews et al., 2008; Ghaemi et al., 2009; Iosifescu et al., 2009; 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, 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 for 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. An improvement was also observed 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 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 an 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 of 14 were randomized controlled trials conducted only with patients with BD, and 3 of them were open label studies. Miskowiak and colleagues (2016) 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 primary outcomes (for 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 that 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 brain derived neurotrophic factor levels compared with 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 and Jimenez concluded that no specific atypical antipsychotic appears better than the others with regard to its cognitive profile (Solé and Jiménez, 2015). Anticonvulsants in bipolar patients seem to exert similar cognitive effects as those described in volunteers and patients with epilepsy (Gualtieri and Johnson, 2006). Lastly, as a whole, antidepressants seem 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 few effects are due to the medication per se (Goswami et al., 2009).

Nonpharmacological Approaches

Prior research on cognitive remediation in schizophrenia has provided some guides for BD. Nevertheless, as mentioned above, 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 develop new interventions specifically addressed to the characteristics of the latter group (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 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 (Deckerbach 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 intervention includes both individual and group format tasks in an ecologic setting 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 with psychoeducation and 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 2 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, 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 brief 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 (2015), cognitive remediation was not effective to ameliorate cognitive dysfunction in partial remitted bipolar patients with a 12-week group-based program. 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 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 (2015) introduced a computer-assisted cognitive training as a part of the cognitive remediation program. Concerning this topic, Lewandowski and colleagues (2016) have published a study protocol for assessing the efficacy of an internet-based cognitive remediation program for patients with BD type I, similarly to Strawbridge and co-workers (Strawbridge et al., 2016). Unfortunately, results of both studies are not available yet.

Because 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, no studies have been exclusively focused on bipolar patients. Lahera and co-workers (2013) assessed the efficacy of the Social Cognition and Interaction Training, an intervention originally developed for patients with schizophrenia, in a sample mostly composed by bipolar patients but also some schizoaffective patients. The intervention, addressed to improve emotion perception, attributional style, and theory of mind, was found to be effective at 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 growing interest in implementing mindfulness-based interventions for the treatment of mental disorders, with some studies focusing on BD. Overall, mindfulness appears as a useful intervention for the reduction of anxiety symptoms and, probably, to reduce depression 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 (2011) provides preliminary results that mindfulness may be an adjunct treatment option to medication to improve cognitive functioning in BD. Likewise, the cognitive remediation program proposed by Demant and colleagues (2015) also included some mindfulness exercises to practice at home and at the beginning of each session as a means to enhance the attentional capacity. 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 the early stages, and further research is needed to find the key components of cognitive and/or functional remediation.

Lastly, some evidence grows concerning the role of noninvasive brain stimulation techniques, such as 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. (2011) 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 with healthy participants. 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. Repetitive sessions of transcranial direct current stimulation (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 visuospatial memory (Minichino et al., 2015). Nevertheless, this study had significant limitations with the lack of a sham control group and a limited neuropsychological assessment. On the other hand, an intra-individual cross-over study failed to prove the efficacy of a single session of tDCS improving working memory and attention in euthymic bipolar patients (Martin et al., 2015). These last results are in contrast to those reported in other studies conducted in 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 with 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.

Other Approaches to Prevent Cognitive Impairment

While research in all these above-mentioned areas proceeds, it is also important that clinicians prevent neurocognitive impairment through different strategies (see Figure 1). 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 (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 toward 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 toward 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). 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, and overweight or obesity (van Corp et al., 1998; Levy et al., 2008; Sanchez-Moreno et al., 2009; Balanzá-Martínez et al., 2010; Yim et al., 2012; Depp et al., 2014; Silva et al., 2014; Lackner et al., 2015; Volkert et al., 2015; 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 in 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 5 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, and mental

### Table 1. Moderators of cognitive deficits in bipolar disorder (BD)

| Variable                                                                 | Description                                                                 |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 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)

| Strategy                                                                 | Description                                                                 |
|-------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 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)       |                                                                            |

Abbreviations: DTMS, deep transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.
and physical activities may also influence it. The most common 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 2-year follow-up of this group of patients (Amoretti et al., 2016). Altogether, these data suggest that interventions to enrich cognitive reserve in the early stages of the illness might result in minimizing the detrimental neuropsychological and functional impact caused (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**

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 the 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 that 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 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 nonchronic 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 kinds of studies may lead to a better definition of subgroups and would provide helpful guidance for developing more effective pharmacological or psychotherapeutic interventions contributing to enhance the management of the illness.

Despite the increase of research investigating new pharmacological and nonpharmacological 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 remain unclear in schizophrenia, with discrepant results (Bobo et al., 2011). Taking 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 narrow 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 BD 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 pro-cognitive 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 the long term. The combination of potential pro-cognitive drugs with cognitive/functional remediation is another path to be explored in bipolar patients, since the combination of both may produce more robust efficacy with cognitive enhancements increasing the physiological mechanisms through which cognitive/functional remediation produces 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, the 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 Consolidated Standards for Reporting Trials (Moher et al., 2010) guidelines for randomized controlled trials, as Miskowiak and colleagues suggested (2016). Burdick and colleagues (2015) also proposed some recommendations for handling important methodological challenges associated with the complexity of the disorder in designing trials to address cognition. 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 impairments and the associated disability.

To implement randomized controlled trials, specifying which neurocognitive battery is optimal to screen for cognitive impairments and the associated disability.

Acknowledgments

The authors thank the support of the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III, CIBERSAM, the Secretaría d’Universitats i Recerca del Departament d’Economia i Coneixement (2014_SGR_398), CERCAProgramme / Generalitat de Catalunya and the 2013 & 2014 NARSAD, Independent Investigator Grant from the Brain & Behavior Research Foundation.

This work was supported by grants from the Spanish Ministry of Economy and Competitiveness (grant nos. P11/00637, P112/00912, P115/00330) PN 2008–2011, Instituto de Salud Carlos III, Subdirección General de Evaluación y Fomento de la Investigación; Fondo Europeo de Desarrollo Regional. Unión Europea, “Una manera de hacer Europa”; CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya (2014 SGR 398 to the Bipolar Disorders Group). Dr. Anabel Martinez-Aran’s project is supported, in part, by a 2013 NARSAD, Independent Investigator Grant from the Brain & Behavior Research Foundation. Dr. Carla Torrent is funded by the Spanish Ministry of Economy and Competitiveness, Instituto Carlos III, through a ‘Miguel Servet’ postdoctoral contract (CP14/00175) and a FIS (PI 12/01498). Dr. Torrent’s project is also supported in part by a 2014 NARSAD, Independent Investigator Grant from the Brain & Behavior Research Foundation (grant number 22039). Dr. I. Grande has received a Juan Rodés Contract (JR15/00012), Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, Barcelona, Spain.

Statement of Interest

Dr. Martinez-Aran has served as speaker or advisor for the following companies: Bristol-Myers Squibb, Otsuka, Lundbeck and Pfizer. Dr. Vieta has received grants, CME-related honoraria, or consulting fees from AB-Biotics, Actavis, Alexza, Almirall, Allergan, AstraZeneca, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo Pharma, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmith-Kline, Janssen, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Qualigen, Roche, Sanofi-Aventis, Schering-Plough, Servier, Shire, Solvay, Sunovion, Takeda, Teléfonica, Teva, the Spanish Ministry of Science and Innovation (CIBERSAM), the Brain and Behavior Foundation, the Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, United Biosource Corporation, and Wyeth. The other authors report no financial relationships with commercial interests. Dr. Carvalho received speaker honoraria from Abbott, GlaxoSmithKline, Lundbeck, Pfizer, and Ache. The other authors report no financial relationships with commercial interests.

References

Alda M, McKinnon M, Blagdon R, Garnham J, MacLellan S, O’Donovan C, Hajek T, Nair C, Dursun S, MacQueen G (2017) Methylene blue treatment for residual symptoms of bipolar disorder: randomised crossover study. Br J Psychiatry 210:54–60.
Amoretti S, Bernardo M, Bonnin CM, Bioque M, Cabrera B, Mezquida G, Sole B, Vieta E, Torrent C (2016) The impact of cognitive reserve in the outcome of first-episode psychoses: 2-year follow-up study. Eur Neuropsychopharmacol 26:1638–1648.
Anaya C, Torrent C, Caballeró FF, Vieta E, Bonnin CM, Ayuso-Mateos JL (2016) Cognitive reserve in bipolar disorder: relation to cognition, psychosocial functioning and quality of life. Acta Psychiatr Scand 133:386–398.

Barts B, Jabben N, Krabbendam L, van Os J (2008) Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol Med 38:771–785.

Balanzá-Martínez V, Rubio C, Selva-Vera G, Martínez-Aran A, Sánchez-Moreno J, Salazar-Fraile J, Vieta E, Tabárés-Seisdedos R (2008) Neurocognitive endophenotypes (endophenocogni-types) from studies of relatives of bipolar disorder subjects: a systematic review. Neurosci Biobehav Rev 32:1426–1438.

Balanzá-Martínez V, Selva G, Martínez-Arán A, Prickaerts J, Sala-Balanzá-Martínez V, Rubio C, Selva-Vera G, Martínez-Aran A, Arts B, Jabben N, Krabbendam L, van Os J (2008) Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol Med 38:771–785.

Berd M, Conus P, Lucas N, Hallam K, Malhi GS, Dodd S, Yatham LN, Yung A, McGorry P (2007) Setting the stage: from pro-drome to treatment resistance in bipolar disorder. Bipolar Disord 9:671–678.

Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaïtiz I, Andersen-Hunt M, Bush AI (2008) N-acetyl cysteine for depressive symptoms in bipolar disorder—a double-blind randomized placebo-controlled trial. Biol Psychiatry 64:468–475.

Berk M, Dean OM, Cotton SM, Gama CS, Kapczinski F, Fernandes B, Kohlmann K, Jeavons S, Hewitt K, Moss K, Allwang C, Schapkaïitz I, Cobb H, Bush AI, Dodd S, Malhi GS (2012) Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo-controlled trial. BMC Med 10:91.

Bobo WV, Woodward ND, Sim MY, Jayathilake K, Meltzer HY (2011) The effect of adjunctive armodafinil on cognitive performance and psychopathology in antipsychotic-treated patients with schizophrenia/schizoaffective disorder: a randomized, double-blind, placebo-controlled trial. Schizophr Res 130:106–113.

Bonnín CM, Martínez-Arán A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, Murru A, Sanchez-Moreno J, Vieta E (2010) Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. J Affect Disord 121:156–160.

Bonnín CM, Sánchez-Moreno J, Martínez-Arán A, Solé B, Reinaires M, Rosa AR, Goikolea JM, Benabarre A, Ayuso-Mateos JL, Ferrer M, Vieta E, Torrent C. (2011) Subthreshold symptoms in bipolar disorder: impact on neurocognition, quality of life and disability. J Affect Disord 136:650–659.

Bonnín CM, Reinares M, Martínez-Aran A, Balança-Martínez V, Sole B, Torrent C, Tabarés-Seisdedos R, García-Portilla MP, Ibañez A, Amann BL, Arango C, Ayuso-Mateos JL, Crespo JM, González-Pinto A, Colom F, Vieta E, CIBERSAM Functional Remediation Group (2015) Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory. Psychol Med 46:291–301.

Bonnín CM, Torrent C, Arango C, Amann BL, Sole B, Gonzalez-Pinto A, Crespo JM, Tabárés-Seisdedos R, Reinares M, Ayuso-Mateos JL, García-Portilla MP, Ibáñez A, Salamero M, Vieta E, Martínez-Aran A; CIBERSAM Functional Remediation Group (2016) Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. Br J Psychiatry 208:87–93.

Bora E (2016) Differences in cognitive impairment between schizophrenia and bipolar disorder: considering the role of heterogeneity. Psychiatry Clin Neurosci 70:424–433.

Bora E, Hidroglu C, Özerdem A, Kaçar ÖF, Sansoy G, Civil Arslan F, Aydemir Ö, Cubukcuoglu Tas Z, Vahip S, Atalay A, Atasoy N, Ateçi F, Tümkaya S (2016a) Executive dysfunction and cognitive subgroups in a large sample of euthymic patients with bipolar disorder. Eur Neuropsychopharmacol 26:1338–1347.

Bora E, Pantelis C (2015) Meta-analysis of cognitive impairment in first-episode bipolar disorder: comparison with first-episode schizophrenia and healthy controls. Schizophr Bull 41:1095–1104.

Bora E, Pantelis C (2016) Social cognition in schizophrenia in comparison to bipolar disorder: a meta-analysis. Schizophr Res 175:72–78.

Bora E, Yucel M, Pantelis C (2009) Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord 113:1–20.

Bora E, Veznedaroğlu B, Vahip S (2016b) Theory of mind and executive functions in schizophrenia and bipolar disorder: a cross-diagnostic latent class analysis for identification of neuropsychological subtypes. Schizophr Res 176:500–505.

Bortolato B, Miskowiak KW, Köhler CA, Vieta E, Carvalho AF (2015) Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. Neuropsychiatr Dis Treat 11:3111–3125.

Bourne C, Aydemir O, Balanza-Martinez V, Bora E, Brissos S, Cavanagh JT, Clark L, Cubukcuoglu Z, Dias VV, Dittmann S, Ferrier IN, Fleck DE, Frangou S, Gallagher P, Jones L, Kieseppä T, Martínez-Arán A, Melle I, Moore PB, Mur M, et al. (2013) Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr Scand 128:149–162.

Breitborde NJ, Dawson SC, Woolverton C, Dawley D, Bell EK, Norman K, Polsinelli A, Bernstein B, Mirsky P, Pletkova C, Grucci F, 3rd, Montoya C, Nanadiego B, Sarabi E, DePalma M, Moreno F (2014) A randomized controlled trial of cognitive remediation and d-cycloserine for individuals with bipolar disorder. BMC Psychol 2:41.

Budde M, Schulze TG (2014) Neurocognitive correlates of the course of bipolar disorder. Harv Rev Psychiatry 22:342–347.

Burdick KE, Braga RJ, Nnadi CU, Shaya Y, Stearns WH, Malhotra AK (2012) Placebo-controlled adjunctive trial of pramipexole in patients with bipolar disorder: targeting cognitive dysfunction. J Clin Psychiatry 73:103–112.

Burdick KE, Russo M, Frangou S, Mahon K, Braga RJ, Shanahan M, Malhotra AK (2014) Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. Psychol Med 44:3083–3096.

Burdick KE, Ketter TA, Goldberg JF, Calabrese JR (2015) Assessing cognitive function in bipolar disorder: challenges and recommendations for clinical trial design. J Clin Psychiatry 76:e342–350.

Catalá-López F, Génova-Maleras R, Vieta E, Tabárés-Seisdedos R (2013) The increasing burden of mental and neurological disorders. Eur Neuropsychopharmacol 23:1337–1339.

Chengappa KN, Bowie CR, Schlicht PJ, Fleet D, Bell K, Mirsky P, Pletkova C, Grucci F, 3rd, Montoya C, Nanadiego B, Sarabi E, DePalma M, Moreno F (2014) A randomized controlled trial of cognitive remediation and d-cycloserine for individuals with bipolar disorder. BMC Psychol 2:41.

Cuthbert BN (2014) The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 13:28–35.
Daban C, Martinez-Aran A, Torrent C, Tabárés-Seisdedos R, Balanzá-Martínez V, Salazar-Fraile J, Selva-Vera G, Vieta E (2006) Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. Psychother Psychosom 75:72–84.

Dean OM, Bush AI, Copolov DL, Kohlmann K, Jeavons S, Schapkatz I, Anderson-Hunt M, Berk M (2012) Effects of N-acetyl cysteine on cognitive function in bipolar disorder. Psychiatry Clin Neurosci 66:514–517.

Deckersbach T, Nierenberg AA, Kessler R, Lund HG, Ameratino RM, Sachs G, Rauch SL, Dougherty D (2010) RESEARCH: cognitive rehabilitation for bipolar disorder: an open trial for employed patients with residual depressive symptoms. CNS Neurosci Ther 16:298–307.

de la Serna E, Vila M, Sanchez-Gistau V, Moreno D, Romero S, Suganyes G, Baeza I, Llorente C, Rodriguez-Toscano E, Sánchez-Gutierrez T, Castro-Fornieles J (2016) Neuropsychological characteristics of child and adolescent offspring of patients with bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 65:54–59.

Demant KM, Vinberg M, Kessing LV, Miskowiak KW (2015) Effects of short-term cognitive remediation on cognitive dysfunction in partially or fully remitted individuals with bipolar disorder: results of a randomised controlled trial. PloS One 10:e0127955.

Depp CA, Strassnig M, Mausbach BT, Bowie CR, Wolyniec P, Thornquist MH, Luke JR, McGrath JA, Pulver AE, Patterson TL, Harvey PD (2014) Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. Bipolar Disord 16:422–431.

Forcada I, Mur M, Mora E, Vieta E, Barrantes-Faz D, Portella MJ (2015) The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder. Eur Neuropsychopharmacol 25:214–222.

Fountoulakis KN, Vieta E, Young A, Yatham L, Grunze H, Bliper P, Moeller HJ, Kasper S (2016) The International College of Neuropsychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 4: unmet needs in the treatment of bipolar disorder and recommendations for future research. Int J Neuropsychopharmacol pii: pyw072 [Epub ahead of print].

Franke AG, Gränsmark P, Agricola A, Schühle K, Rommel T, Sebastian A, Balló HE, Gorbulev S, Gerdes C, Frank B, Ruckes C, Tüscher O, Lieb K (2017) Methylphenidate, modafinil, and caffeine for cognitive enhancement in chess: a double-blind, randomised controlled trial. Eur Neuropsychopharmacol 27:248–260.

Fuentes-Durá I, Balanzá-Martínez V, Ruiz-Ruiz JC, Martínez-Arán A, Girón M, Solé B, ánchez-Moreno J, Gómez-Beneyto M, Vieta E, Tabárés-Seisdedos R (2012) Neuropsychological training in patients with bipolar disorders: current status and perspectives. Psychother Psychosom 81:250–252.

Ghaemi SN, Gilmer WS, Dunn RT, Hanlon RE, Kemp DE, Bauer AD, Chiriki I, Filkowski MM, Harvey PD (2009) A double-blind, placebo-controlled pilot study of galantamine to improve cognitive dysfunction in minimally symptomatic bipolar disorder. J Clin Psychopharmacol 29:291–295.

Gildengers AG, Butters MA, Chisholm D, Reynolds CF, Mulsant BH (2008) A 12-week open-label pilot study of donepezil for cognitive functioning and instrumental activities of daily living in late-life bipolar disorder. Int J Geriatr Psychiatry 23:693–698.

Goodwin GM, Martinez-arana A, Glahn DC, Vieta E (2008) Cognitive impairment in bipolar disorder: neurodevelopment or neurodegeneration? An ECNP expert meeting report. Eur Neuropsychopharmacol 18:787–793.

Goss AJ, Kaser M, Costafreda SG, Sahakian BJ, Fu CH (2013) Modafinil augmentation therapy in unipolar and bipolar depression: a systematic review and meta-analysis of randomised controlled trials. J Clin Psychiatry 74:1101–1107.

Goswami U, Sharma A, Varma A, Gurlajani C, Ferrier IN, Young AH, Gallagher F, Thompson JM, Moore PB (2009) The neurocognitive performance of drug-free and medicated euthymic bipolar patients do not differ. Acta Psychiatr Scand 120: 456–465.

Grande I, Berk M, Birmaher B, Vieta E (2016) Bipolar disorder. Lancet 387:1561–1572.

Grande I, Sanchez-Moreno J, Sole B, Jimenez E, Torrent C, Bonnin CM, Varo C, Tabares-Seisdedos R, Balanzá-Martínez V, Valls E, Morilla I, Carvalho AF, Ayuso-Mateos JL, Vieta E, Martinez-Aran A (2017) High cognitive reserve in bipolar disorders as a moderator of neurocognitive impairment. J Affect Disord 208:621–627.

Gualtieri CT, Johnson LG (2006) Comparative neurocognitive effects of 5 psychotropic anticonvulsants and lithium. MedCenMed 8:46.

Harel EV, Zangen A, Roth Y, Reti I, Braw Y, Levkovitz Y (2011) H-coil repetitive transcranial magnetic stimulation for the treatment of bipolar depression: an add-on, safety and feasibility study. World J Biol Psychiatry 12:119–126.

Hellvin T, Sundet K, Simonsen C, Aminoff SR, Lagerberg TV, Assendean OA, Melle I (2012) Neurocognitive functioning in patients recently diagnosed with bipolar disorder. Bipolar Disord 14:227–238.

Iosifescu DV, Moore CM, Deckersbach T, Tilley CA, Ostacher MJ, Sachs GS, Nierenberg AA (2009) Galantamine-ER for cognitive dysfunction in bipolar disorder and correlation with hippocampal neuronal viability: a proof-of-concept study. CNS Neurosci Ther 15:309–319.

Jensen JH, Knorr U, Vinberg M, Kessing LV, Miskowiak KW (2016) Discrete neurocognitive subgroups in fully or partially remitted bipolar disorder: associations with functional abilities. J Affect Disord 205:378–386.

Kapcinski F, Vieta E, Cristina A, Frey BN, Gomes FA, Tramontina J, Kauer-Sant’anna M, Grassi-Oliveira R, Post RM (2008) Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev 32:675–692.

Kaser M, Deakin JB, Michael A, Zapata C, Bansal R, Ryan D, Cormack F, Rowe JB, Sahakian BJ (2017) Modafinil improves episodic memory and working memory cognition in patients with remitted depression: a double-blind, randomized, placebo-controlled study. Biol Psychiatr Cognitive Neuroscience and Neuroimaging 2:115–122.

Keefe RS, McClintock SM, Roth RM, Doraiswamy PM, Tiger S, Madhoo M (2014) Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review. J Clin Psychiatry 75:864–876.

Kozicky JM, Torres IJ, Silveira LE, Bond DJ, Lam RW, Yatham LN (2014) Cognitive change in the year after a first manic episode: association between clinical outcome and cognitive performance early in the course of bipolar I disorder. J Clin Psychiatry 75:e587–93.

Kucy A, Alsuwaidan MT, Liauw SS, McNulty RS (2010) Aerobic physical exercise as a possible treatment for neurocognitive dysfunction in bipolar disorder. Postgrad Med 122:107–116.

Kurtz MM, Gerraty RT (2009) A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology 23:551–562.
Lackner N, Bengesser SA, Birner A, Painold A, Fellendorf FT, Platzer M, Reininghaus B, Weiss EM, Mangge H, McIntyre RS, Fuchs D, Kaphammer HP, Wallner-Liebmann SJ, Reininghaus EZ (2015) Abdominal obesity is associated with impaired cognitive function in euthymic bipolar individuals. World J Biol Psychiatry 17:535–546.

Lahera G, Ruiz-Murugarren S, Iglesias P, Ruiz-Bennasar C, Montes M, Ferna A (2012) Social cognition and global functioning in bipolar disorder. J Nerv Ment Dis 200:135–141.

Lahera G, Benito A, Montes JM, Fernandez-Liria A, Obert CM, Penn DL. (2013) Social cognition and interaction training (SCIT) for outpatients with bipolar disorder. J Affect Disord 146:132–136.

Lee RSC, Hermens DF, Scott J, Redoblado-Hodge MA, Naismith SL, Lagopoulos J, Griffiths KR, Porter MA, Hickie IB (2014). A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. J Psychiatr Res 57:1–11.

Levy B, Monzani BA, Stephansky MR, Weiss RD (2008) Neurocognitive impairment in patients with co-occurring bipolar disorder and alcohol dependence upon discharge from inpatient care. Psychiatry Res 161:28–35.

Lewandowski KP, Sperry SH, Ongur D, Cohen BM, Norris LA, Keshavan MS (2016) Cognitive remediation versus active computer control in bipolar disorder with psychosis: study protocol for a randomized controlled trial. Trials 17:136.

Lichtenstein P, Yip BH, Björk C, Pawanit TD, Sullivan PF, Hultman CM (2009) Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373:234–239.

López-Jaramillo C, Lopera-Vásquez J, Gallo A, Ospina-Duque J, Bell V, Torrent C, Martínez-Aran A, Vieta E (2010). Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disord 12:557–567.

Malchow B, Reich-Erkelenz D, Oertel-Knochel V, Keller K, Hasan A, Schmitt A, Scheewe TW, Cahn W, Kahn RS, Falkai P (2013) The effects of physical exercise in schizophrenia and affective disorders. Eur Arch Psychiatry Clin Neurosci 263:451–467.

Marshall DF, Passarotti AM, Ryan KA, Kamali M, Saunders EFH, Pester B, McNinn MG, Langenecker SA (2016) Deficient inhibitory control as an outcome of childhood trauma. Psychiatry Res 235:7–12.

Martin DM, Chan H, Green MJ, Mitchell PB, Alonzo A, Loo C (2015) Transcranial direct current stimulation (tDCS) to remediate cognitive function in euthymic bipolar disorder patients. Bipolar Disord 17:849–858.

Martínez-Aran A, Vieta E (2015) Cognition as a target in schizophrenia, bipolar disorder, and depression. Eur Neuropsychopharmacol 25:151–157.

Martino DJ, Samamé C, Ibañez A, Streijlevich SA (2015) Neurocognitive functioning in the premorbid stage and in the first episode of bipolar disorder: a systematic review. Psychiatry Res 226:23–30.

Matthews JD, Blais M, Park L, Welch C, Baity M, Murakami J, Sklar sky K, Homberger C, Fava M (2008) The impact of galantamine on cognitive function and mood during electroconvulsive therapy: a pilot study. J Psychiatr Res 42:526–531.

Matthews JD, Sievert CJ, Blais MA, Park LT, Sievert CJ, Welch CA, Dubois CM, van Nuenenhuizen AO, Rooney KO, Seabrook RC, Durham LE, Adams HC, Fava M (2013) A double-blind, placebo-controlled study of the impact of galantamine on anterograde memory impairment during electroconvulsive therapy. J ECT 29:170–178.

McIntyre RS, Soczynska JK, Woldeyohannes HO, Miranda A, Vaccarino A, Macqueen G, Lewis G, Kennedy SH (2012) A randomized, double-blind, controlled trial evaluating the effect of intranasal insulin on neurocognitive function in euthymic patients with bipolar disorder. Bipolar Disord 14:697–706.

Milan MJ, Goodwin GM, Meyer-Lindenberg A, Ove Ögren S (2015) Learning from the past and looking to the future: emerging perspectives for improving the treatment of psychiatric disorders. Eur Neuropsychopharmacol 25:599–656.

Minichino A, Bersani FS, Capra E, Fannese R, Bonanno C, Salvati M, Delle Chiaie R, Biondi M (2012) ECT, rTMS, and deepTMS in pharmacoresistant drug-free patients with unipolar depression: a comparative review. Neuropsychiatr Dis Treat 8:55–64.

Minichino A, Bersani FS, Bernabei L, Spagnoli F, Vergnani L, Corrado A, Taddei I, Biondi M, Delle Chiaie R (2015) Prefrontocerebellar transcranial direct current stimulation improves visuospatial memory, executive functions, and neurological soft signs in patients with euthymic bipolar disorder. Neuropsychiatr Dis Treat 11:2265–2270.

Miskowiak KW, Ehrenreich H, Christensen EM, Kessing LV, Vinberg M (2014) Recombinant human erythropoietin to target cognitive dysfunction in bipolar disorder: a double-blind, randomized, placebo-controlled phase 2 trial. J Clin Psychiatry 75:1347–1355.

Miskowiak KW, Carvalho AF, Vieta E, Kessing LV (2016) Cognitive enhancement treatments for bipolar disorder: a systematic review and methodological recommendations. Eur Neuropsychopharmacol 26:1541–1561.

Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Ellbourne D, Egger M, Altman DG (2010) CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 340:c869.

Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F (2016) Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr Scand 134:91–103.

Rapado-Castro M, Dodd S, Bush AI, Malhi GS, Skvarc DR, On ZX, Berk M, Dean OM (2016) Cognitive effects of adjunctive N-acetyl cysteine in psychosis. Psychiatr Med 29:1–11.

Reinares M, Sánchez-Moreno J, Fountoulakis KN (2014) Psycho-social interventions in bipolar disorder: what, for whom, and when. J Affect Disord 156:46–55.

Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, Moore PB (2006) A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord 93:105–115.

Rosa AR, Magalhães PVS, Czeplelewski L, Sulzbach MV, Goi PD, Vieta E,Gama CS, Kapczinski F (2014) Clinical staging in bipolar disorder: Focus on cognition and functioning. J Clin Psychi atry 75:450–456.

Rosenblat JD, Kakar R, McIntyre RS (2015) The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol 19:1–13.

Rybakowski JK, Suwalska A (2010) Excellent lithium responders and microbiota. Rev Psiquiatr Salud Ment. Mar 22. pii: S1888-9891(17)30029-0. doi: 10.1016/j.rpsm.2017.02.001.
Samamé C, Martino DJ, Strejilevich SA (2014) Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. J Affect Disord 164:130–138.

Samamé C, Martino DJ, Strejilevich SA (2015) An individual task meta-analysis of social cognition in euthymic bipolar disorders. J Affect Disord 173:146–153.

Sanches M, Bauer IE, Galvez JF, Zunta-Soares GB, Soares JC (2015) The management of cognitive impairment in bipolar disorder: current status and perspectives. Am J Ther 22:477–486.

Sanchez-Moreno J, Martinez-Aran A, Colom F, Scott J, Tabares-Seisdedos R, Sugranyes G, Torrent C, Daban C, Benabarre A, Goikolea JM, Franco C, Gonzalez-Pinto A, Ayuso-Mateos JL, Vieta E (2009) Neurocognitive dysfunctions in euthymic bipolar patients with and without prior history of alcohol use. J Clin Psychiatry 70:1120–1127.

Sanchez-Moreno J, Bonnin C, Gonzalez-Pinto A, Amann BL, Solé B, Balanzá-Martinez V, Arango C, Jimenez E, Tabárés-Seisdedos R, Garcia-Portilla MP, Ibañez A, Crespo JM, Ayuso-Mateos JL, Vieta E, Martinez-Aran A, Torrent C. CIBERSAM Functional Remediation Group (2017) Do patients with bipolar disorder and subsyndromal symptoms benefit from functional remediation? A 12-month follow-up study. Eur Neuropsychopharmacol. Advance online publication. Jan 23. pii: S0924-977X(17)30024-X. doi: 10.1016/j.euroneuro.2017.01.010.

Sanchez-Moreno J, Martinez-Aran A, Vieta E (2017) Treatment of cognitive impairment in patients with bipolar disorder. Curr Psychiatry Rep 19:3.

Silva KL, Rovaris DL, Guimarães-da-Silva PO, Victor MM, Salgado CA, Vitola ES, Contini Y, Bertuzzi G, Picon FA, Karam RG, Belzequer JD, Roquezo JA, Roquezo JA, Roquezo JA, Roquezo JA, Roquezo JA. (2017) Meta-analysis of social cognition in euthymic bipolar disorder: who is cognitively impaired and who is preserved. Eur Psychiatry 86:31–46.

Solé B, Bonnin CM, Mayoral M, Amann BL, Torres I, González-Pinto A, Jimenez E, Crespo JM, Colom F, Tabárés-Seisdedos R, Reinares M, Ayuso-Mateos JL, Soria S, Garcia-Portilla MP, Ibañez A, Vieta E, Martinez-Aran A, Torrent C. CIBERSAM Functional Remediation Group (2015) Functional remediation for patients with bipolar II disorder: improvement of functioning and subsyndromal symptoms. Eur Neuropsychopharmacol 25:257–264.

Solé B, Jiménez E (2015) Tratamiento antipsicótico y aspectos neurocognitivos. Psiquiatria Biologica 22:36–38.

Solé B, Jiménez E, Torrent C, Bonnin CM, Torres I, Reinares M, Reinares M, Priego Á, Salamero M, Colom F, Varo C, Vieta E, Martinez-Arán A (2016) Cognitive variability in bipolar II disorder: who is cognitively impaired and who is preserved. Bipolar Disord 18:288–299.

Stange JP, Eisner LR, Hözel BK, Peckham AD, Dougherty DD, Rauch SL, Nierenberg AA, Lazar S, Deckersbach T (2011) Mindfulness-based cognitive therapy for bipolar disorder: effects on cognitive functioning. J Psychiatr Pract 17:410–419.

Stern Y (2009) Cognitive reserve. Neuropsychologia 47:2015–28.

Strawbridge R, Fish J, Halarí R, Hodson J, Reeder C, Macritchie K, McCrone P, Wykes T, Young AH (2016) The Cognitive Remediation in Bipolar (CRIB) pilot study: study protocol for a randomised controlled trial. Trials 17:371.

Torrønt C, Martinez-Árán A, Bonnin CM, Reinares M, Daban C, Solé B, Rosa AR, Tabárés-Seisdedos R, Popovic D, Salamero M, Vieta E (2012) Long-term outcome of cognitive impairment in bipolar disorder. J Clin Psychiatry 73:e899–e905.

Torrønt C, et al. (2013) Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. Am J Psychiatry 170:852–859.

Torres JJ, Defreitas VG, Defreitas CM, Anna MK, Bond DJ, Honer WG, Lam RW, Yatham LN (2010) Neurocognitive functioning in patients with bipolar I disorder recently recovered from a first manic episode. J Clin Psychiatry 71:1224–1242.

Tse S, Chan S, Ng KL, Yatham LN (2014) Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder. Bipolar Disord 16:217–229.

van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W (1998) Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. Arch Gen Psychiatry 55:41–6.

Vieta E (2015) Staging and psychosocial early intervention in bipolar disorder. Lancet Psychiatry 2:483–485.

Vieta E (2016) DSM-5.1. Acta Psychiatr Scand 134:187–188.

Volkert J, Kopf J, Kazmaier J, Glaßer F, Zierhut KC, Schiele MA, Kittel-Schneider S, Reif A (2015) Evidence for cognitive subgroups in bipolar disorder and the influence of subclinical depression and sleep disturbances. Eur Neuropsychopharmacol 25:192–202.

Watson S, Gallagher P, Porter RJ, Smith MS, Herron LJ, Bulmer S, North-East Mood Disorders Clinical Research Group., Young AH, Ferrier IN (2012) A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. Biol Psychiatry 72:943–949.

Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ (2009) Effects of lithium on cognitive performance: a meta-analysis. J Clin Psychiatry 70:1588–1597.

Yager J, Feinstein RE (2016) Potential applications of the National Institute of Mental Health’s Research Domain Criteria (RDoC) to Clinical psychiatric practice: how RDoC might be used in assessment, diagnostic processes, case formulation, treatment planning, and clinical notes. J Clin Psychiatry Dec 20. doi: 10.4088/JCP.15nr10476.

Yatham LN, Mackala S, Basivireddy J, Ahn S, Walji N, Hu C, Lam RW, Torres IJ (2017) Lurasidone versus treatment as usual for cognitive impairment in euthymic patients with bipolar I disorder: a randomised, open-label, pilot study. Lancet Psychiatry 4:208–217.

Yim CY, Szczyznka JK, Kennedy SH, Woldeyohannes HO, Brietzke E, McIntyre RS (2012) The effect of overweight / obesity on cognitive function in euthymic individuals with bipolar disorder. Eur Psychiatry 27:223–228.

Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN (2004) Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. Neuropsychopharmacology 29:1538–1545.

Zyto S, Jabben N, Schulte PF, Regeer BJ, Kupka RW (2016) A pilot study of a combined group and individual functional remediation program for patients with bipolar i disorder. J Affect Disord 194:9–15.