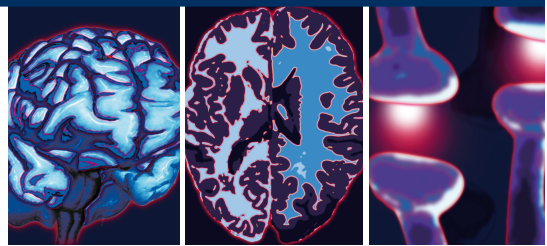# Neurocognitive impairment in the bipolar spectrum

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Practice points

- Neurocognitive deficits are present across the main bipolar disorder (BD) subtypes (BD-I and BD-II), but some deficits are of lesser magnitude in BD-II.

- The main neurocognitive deficits in BD have been found in the attention, memory and executive function domains.

- Several factors can influence neurocognition in BD, such as the chronicity, education, mood state, substance abuse, medications and history of psychosis, as well as subdepressive symptoms.

- More research is needed to ascertain whether cyclothymia and BD not otherwise specified are associated with neurocognitive dysfunction.

- Neurocognitive deficits may have several implications for the functional outcome of BD patients.

- Functional remediation may be a promising intervention in order to improve neurocognitive deficits, as well as functioning, in BD patients.

SUMMARY Neurocognitive impairment is a core deficit of bipolar disorder (BD) since it persists into remission. The aim of this review is to provide an overview of the main neurocognitive disturbances found in the bipolar spectrum. An extensive review of the literature has been carried out for the different subtypes of BD (BD-I, BD-II, BD not otherwise specified, cyclothymia and schizoaffective disorder). Findings from this extensive review suggest that deficits are present across the whole bipolar spectrum (BD-I and BD-II), but some neurocognitive deficits are of lesser magnitude in BD-II. Other subtypes, such as BD not otherwise specified and cyclothymia, deserve more research concerning their effects on neurocognition. Given the correlation between neurocognitive impairment and difficulties in functioning, it may be useful to develop neurocognitive remediation strategies adapted to BD that are aimed at preventing cognitive impairment and restoring the psychosocial functioning of the patient.

Future Medicine part of fsg

Bipolar disorder (BD) is a chronic mental illness that affects approximately 4.4% of the general population [1]. It is associated with neurocognitive impairment, a core deficit that is related to deficits in attention or memory, executive function (EF) and working memory (WM), among others. The neurocognitive deficits appear to persist into remission and have been reported in several studies conducted in euthymic bipolar patients [2–6]. The prevalence of cognitive impairment is approximately 40–60% in BD patients at a level deemed to be clinically relevant [7,8]. Furthermore, in most patients with BD, the deficits are increased as a consequence of the course of the illness, including predictive factors such as the number of manic episodes, hospitalizations and length of illness [9].

Neurocognitive impairment is often characterized as a trait feature of the illness; it also exists in both subtypes of BD, although it has a higher prevalence in BD-I [10]. In this regard, a large number of manic episodes may predict poor neurocognitive performance, suggesting that the recurrence of mania may have a long-term neuropsychologial impact [11]. Something similar occurs in BD-II; the importance of subdepressive symptoms in this group probably has a negative impact in neuropsychological impairment and functioning [12–16].

The aim of this review is to identify the neuropsychological differences between BD-I, BD-II and cyclothymic patients concerning the bipolar spectrum, and the impact or limitations entailed by these conditions on the patients' functioning. The hypothesis is that deficits are more severe in BD-I patients when compared with BD-II or with healthy control subjects, and that neurocognitive impairment may be present, to a lesser degree, in the remaining disorders of the bipolar spectrum.

Method

We conducted a systematic search of the literature on NIH PubMed and Scopus for the last 10 years (from 2000 to 2011). The keywords included in the search were: bipolar disorder type I, bipolar disorder type II, schizoaffective disorder (SZA), bipolar disorder not otherwise specified (BD-NOS) and cyclothymia, crossreferenced with cognitive, neurocognitive, neuropsychological, EF, attention, WM, processing speed, verbal memory, visual memory and verbal fluency. The main neurocognitive tests and neurocognitive domains involved are shown in **Table 1**.

The search only includes original articles with adults, as well as review articles and meta-analyses. All patients included in the studies have met the DSM-IV criteria for BD-I, BD-II or BD-NOS, cyclothymia or SZA. Each group had to be compared with healthy control subjects, or BD-I versus BD-II, BD-I versus a healthy control group or BD-II versus a healthy control group. We excluded letters, editorials, books, case reports, pediatric and childhood subjects and studies that did not evaluate neurocognition in bipolar patients. In addition, we excluded the studies not using standardized neurocognitive tasks or established normative data. References from identified articles were also reviewed to ensure that all relevant papers were included.

■ Neurocognitive impairment in BD-I

There are a large proportion of patients that could not achieve premorbid levels of functioning after the resolution of manic or depressive episodes. Most of them present neuropsychological impairment persisting even in euthymia, which may be a contributing factor for a poor psychosocial functioning. 'Functioning' is a complex concept, since it involves the capacity to work, study, live independently and conduct relationships [17,18]. There is a strong correlation between neurocognition and functioning, so that persistent neurocognitive deficits are reflected in quality of life, work performance, self-esteem and psychosocial functioning [19,20]. In this regard, functional impairment, particularly in the areas of independent living, personal relationships and vocational success, is very common in BD [21]. A recent review pointed out that only 19–23% of adult BD-I patients were married (vs 60% of adults in the general population); 19–58% were not living independently and were usually residing with family members; 57–65% were unemployed (vs 6% of the general population); and up to 80% were considered to have at least partial vocational disability [22,23]. Similarly, in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), 82% had some college education compared with 52% in the general US population, but 37% were unemployed or disabled compared with 3.7% of the contemporaneous general population from a sample of 1000 subjects [24]. Finally, in a recent study that analyzed days out of role due to common physical and mental conditions, the findings were that individuals with BD had one of the most disabling conditions [25].

Table 1. The main neuropsychological tests used in bipolar disorder research.		
Neuropsychological test	**Description**	**Cognitive domain**
Continuous Performance Test	A computerized attention task in which an individual is asked to respond to all letters flashing on the computer screen except for a target letter	Sustained attention/vigilance
WAIS Digit Span Forwards	Subjects repeat a fixed random series of numbers of increasing length in direct order	Attention
WAIS Digit Span Backwards	Subjects repeat a fixed random series of numbers of increasing length in reverse order	Working memory
Trail-Making Test – part A	Subjects use a pencil to connect a series of 25 encircled numbers in numerical order	Attention Processing speed
Trail-Making Test – part B	Subjects connect 25 encircled numbers and letters in numerical and alphabetical order, alternating between the numbers and letters	Executive function Working memory Processing speed
WAIS Digit Symbol	Subjects fill in symbols beneath numbers according to a digit/symbol key as rapidly as possible for 120 s	Processing speed
Category Fluency (Animal Naming)	Subjects name as many animals as possible within 1 min	Frontal executive function Processing speed
Letter Fluency (FAS Controlled Oral Word Association)	Subjects name as many words as possible within 1 min and are instructed not to use proper nouns, numbers or morphological variations of words	Frontal executive function Processing speed
Stroop Color-Word Test	Part 1 consists of reading color names in black ink. Part 2 requires the subjects to say the color of colored 'XXXs'. In part 3, the color words are printed in incongruent ink colors, and the subjects are asked to name the color instead of reading the color word. The subjects have to suppress a habitual response in favor of an unusual one	Executive function Attention Processing speed
Wisconsin Card Sorting Test	Subjects are required to match a series of 128 cards to one of four stimulus cards. Subjects are not told which criterion to use (color, number or shape), only whether the card is placed in the correct or incorrect category. The categorization rule shifts after ten consecutive correct placements and subjects have to search for the new rule	Executive function
Hayling Sentence Completion Task	Examiner reads out 15 sentences with the last word missing. In the first section (response initiation), the sentence must be completed with a single word that is contextually predicted. In the second section (response inhibition), the word given has to be totally unconnected	Executive function
Go/No-Go Task	Participants are required to perform an action given certain stimuli (e.g., press a button – Go) and inhibit that action under a different set of stimuli (e.g., not press that same button – No-Go)	Executive function Attention
CANTAB: Intradimensional/ Extradimensional Set Shifting	The test has nine stages that progress from a simple discrimination of two shapes to a compound discrimination between two pink shapes and two white lines through to an intradimensional shift that requires subjects to maintain their response to shapes rather than lines, and finally to an extradimensional shift that requires subjects to shift their attention to the lines. The subjects progress to a subsequent stage by making six consecutive correct responses within 50 trials	Executive function
WAIS Letter–Number Sequencing	Patients are required to listen to an auditory presentation of alternating numbers and letters and then repeat back the numbers in ascending order, followed by the letters alphabetically	Working memory
California Verbal Learning Test	Verbal learning: list-learning task (16 words, four words from each of four semantic categories). There are five immediate free recall trials of list A followed by an interference list B that is presented once. Verbal recall: short-delay recall of list A is tested in both free and cued forms. Cues are given in the form of the four categories. Following 20 min of nonverbal tests, long delay-free and cued recalls from list A are recorded	Verbal learning and memory
Rey Auditory Verbal Learning Test	Verbal learning: five presentations of lists of 15 words followed by free recall on each trial. Recall: free recall of the words from the original list	Verbal learning and memory
CANTAB: Cambridge Neuropsychological Test Automated Battery; WAIS: Wechsler Adult Intelligence Test – Revised; WMS: Wechsler Memory Scale.		

Table 1. The main neuropsychological tests used in bipolar disorder research (cont.).		
Neuropsychological test	Description	Cognitive domain
Hopkins Verbal Learning Test	A list of 12 nouns (targets) with four words drawn from each of three semantic categories. The tasks include three learning trials, a delayed recall trial (20–25-min delay) and a yes/no delayed recognition trial	Verbal learning and memory
Rey–Osterrieth Complex Figure	Patients are required to make a copy of a complex figure to the best of their ability Recall: reproduction of the drawing from memory some minutes later	Visual Learning and memory
WMS Visual Reproduction	Four line drawings are presented. After the drawing is removed, the subjects are asked to immediately draw the figure from memory. The subjects are asked to draw the four items from memory after a 30-min delay, with no prompts or cues provided	Visual learning and memory
WAIS Vocabulary	The examiner asks the meaning of 40 words, arranged in order of difficulty	Premorbid IQ
National Adult Reading Test	Comprises 50 stimulus words that cannot be pronounced by using common rules of phonetic interpretation. Subjects are required to read each word aloud, and their pronunciation is scored as either right or wrong in accordance with a pronunciation guide	Premorbid IQ
CANTAB: Cambridge Neuropsychological Test Automated Battery; WAIS: Wechsler Adult Intelligence Test – Revised; WMS: Wechsler Memory Scale.		

The domains that best define the neurocognitive deficits in BD-I are verbal memory [26–32], EF [26,31,33–37] and attention [15,33–35,38]. However, the affected neurocognitive domains are not consistent in all studies [39,40].

General intellectual function (IQ)

Overall, no significant differences in general intellectual function were found between the different groups (BD-I vs healthy control group; BD-I vs BD-II; and BD-I patients with differing numbers of manic episodes) [4,24,41–44].

Concerning BD-II, subjects have normal general intellectual function [30,45–53]. Only one report found that bipolar patients (BD-I and BD-II) differed significantly from healthy subjects [54]. Regarding this characteristic, an interesting study found that BD-II patients presented a greater intellectual decline compared with BD-I patients using an index of IQ change (difference between actual and premorbid IQ), suggesting that depression may represent a risk factor that could lead to the development of neurocognitive abnormalities [55]. However, these findings have not been replicated.

Learning & memory

The measures related to verbal learning and recall/recognition are generally assessed by tests that include word lists, story recall and recognition tasks. In a prospective 15-year follow-up study including a sample of 33 bipolar patients, Burdick *et al.* assessed affective symptoms, neurocognition, global functioning and work and social adjustment, and found that patients with BD showed significant deficits in verbal learning

and memory [56]. When comparing the BD-I with BD-II subtypes, BD-I subjects demonstrated a lower performance than BD-II subjects in some measures of verbal memory assessed by the California Verbal Learning Test [10,57]. The study by Martinez-Aran *et al.* included acute and remitted patients [57], whereas Torrent *et al.* assessed only euthymic patients [10]. In addition, some studies comparing euthymic BD-I subjects with a healthy control group observed the same results, in which BD-I subjects demonstrated a worse performance [4,42,43]. The difference between these studies is that Jamrozinski and colleagues studied whether patients with or without antipsychotic drug use differed significantly from healthy controls in any neuropsychological measure, and only patients treated with antipsychotics showed an underperformance in verbal memory [43]. Moreover, residual depressive symptoms are positively correlated with poor performance in this domain [4]. Finally, there is a significant difference between the genders; BD-I males showed a poorer performance in immediate memory, particularly in processes related to encoding and retrieval, when compared with females [58].

With regard to visual memory, few studies reported impairment in this domain [42,54,59]. Some differences were found between the last two studies. On the one hand, Dittmann *et al.* found that both groups, BD-I and BD-II, performed significantly worse than the control group [54]; on the other hand, Summers *et al.* found that BD-II subjects did worse than BD-I subjects [59]. Nevertheless, they noticed that a poor performance in BD-II subjects with

respect to the BD-I subjects was related to scores on the Beck Inventory for Depression only in the forms–shapes test. No differences have been detected in visual memory between BD-I patients with or without history of psychosis [41].

EF & WM

EF represents the capacity to solve mental and environmental problems. EF includes WM, decision making, planning, monitoring and inhibition behaviors. Many researchers found that these functions are altered in BD. Similarly, WM involves mental structures and processes that are responsible for storing and actively maintaining a limited amount of information and handling this information for execution of more complex constructs.

Goswami *et al.* observed that bipolar patients demonstrated a worse performance than the control group [4]. Furthermore, Torrent *et al.* detected that subjects with BD-I or BD-II with longer illness durations showed more difficulties in tasks of WM, such as the Digit Span Backwards subtest [10]. However, in the group studied by Summers *et al.*, the BD-II subjects demonstrated poorer performance than BD-I subjects [59]. In the same vein, suicidal attempts in depressive patients were also found to be associated with a poorer WM performance by both subtypes; these BD-II subjects were comparatively worse in two WM measures (A-not-B Reaction Time and N-Back tests) while these BD-I subjects were only worse in one of them (A-not-B Reaction Time Test) [52]. However, Torres *et al.* did not demonstrate significant findings regarding neurocognitive measures and symptom ratings [44]. In conclusion, these differences could indicate a reduction in WM.

Next, regarding verbal fluency, Lopez-Jaramillo *et al.* designed a study comparing BD-I subjects with a healthy control group and found significant differences in phonetic and semantic verbal fluency; moreover, those patients who had experienced three or more manic episodes demonstrated major deficits in this domain compared with those who had experienced just one [42]. In the same vein, Balanza-Martinez *et al.* compared the neurocognitive impairment in BD-I subjects with schizophrenic patients over a 3-year follow-up study and found that schizophrenic and bipolar patients showed significantly poorer performances than healthy subjects on most of the neurocognitive tasks, as well as in verbal fluency [26]. Finally, most of the studies assessing semantic verbal fluency found that BD-I patients performed worse than control subjects [10,26,30,42,54].

With regard to cognitive flexibility, Carrus *et al.* did not find an effect of diagnosis (F = 2.17; df = 2, 74; p = 0.12) or gender (F = 0.35; df = 2, 74; p = 0.70) or gender by diagnosis interaction (F = 0.51; df = 2, 74; p = 0.60) for the Wisconsin Card Sorting Test (WCST) categories and perseverative errors [58]. Similarly, other researchers did not find any differences between BD-I subjects and control groups [4,56]. In addition, patients without antipsychotic treatment performed significantly better than patients using antipsychotics in all neurocognitive measures, except for the WCST [43]. Lopez-Jaramillo and colleagues suggested that patients with more manic episodes showed psychomotor slowing in tests of executive attention, such as the Trail-Making Test part B (TMT-B) [42]. Euthymic BD-I patients with a history of psychosis demonstrated poorer results in the WCST and Stroop test than patients without such a history [41]. When authors took into account the bipolar subtype, they found that BD-II subjects performed worse than BD-I subjects in the TMT-B [59,60]. However, Torrent *et al.* found that BD-II as well as BD-I subjects showed a trend towards more perseverative errors on the WCST when compared with control groups, which could be related to greater impulsivity [10].

Attention & psychomotor speed

With regard to attention and psychomotor speed in BD-I, different studies support the hypothesis that BD-I patients have difficulties in attention and psychomotor speed [10,54]. For instance, Torres *et al.* detected deficits in attention in clinically stable patients with BD-I very early in the course of illness [44]. Furthermore, attention deficits were detected when comparing the group of patients with one manic episode to the group with three or more episodes [42]. When comparing each patient group with the control group, the authors also found that patients with three or more manic episodes show significant differences in attention compared with those who had just one manic episode. The recurrence of mania, therefore, may have a long-term neuropsychological impact. However, Goswami *et al.* did not detect differences in this domain between euthymic BD-I subjects and healthy controls [4].

When comparing the BD-I and BD-II groups, both performed worse than control groups on attention (TMT-A and Digit Span Forwards tests) [10,54]. In addition, processing speed is robustly associated with social and global functioning in BD [37,56]. Poor work functioning is significantly related to subsyndromal depression and the course of illness [56]. However, others did not find significant differences between both diagnostic subtypes in attention and processing speed [4,24,43,44,59].

■ **Neurocognitive impairment in BD-II**
The field of neurocognition that specifically focused on the BD-II subtype has been developed to a lesser extent than the BD-I subtype, probably due to the fact that the former is an underdiagnosed subtype. Moreover, fewer studies have been conducted with remitted BD-II patients, limiting the generalization of findings to all the BD-II population. Nevertheless, a recent systematic review and a meta-analysis have been published, suggesting that BD-II patients are not free of neurocognitive impairment [60,61], displaying subtle differences when compared with BD-I patients.

In the following sections, we will detail the main neurocognitive findings in this subtype, with a greater emphasis on euthymic bipolar patients.

Learning & memory
Learning and verbal memory dysfunction seem to be present in BD-II subjects; however, it appears to be more specifically associated with the BD-I subtype, as has been proposed by a meta-analytic review [61]. Several studies found deficits in memory in BD-II patients [47,53]. Nevertheless, other researchers detected a significantly worse performance in BD-I participants, but not in those with BD-II [30,48,50,54,62]. Two reports pointed out that a history of psychosis explained more of the neurocognitive variance than diagnostic subtype [29,63], which could be related to the more severe memory dysfunction detected in BD-I patients. Recently, a meta-analytic study suggested that a history of psychosis in patients is modestly associated with greater severity of neurocognitive impairment in BD, although psychosis cannot fully explain the neurocognitive deficits in BD [64]. Another possible explanation could be related to the neurotoxic effect of manic episodes rather than depressive ones [65]. Thus, discrepant findings in studies could be explained by differences in methodology, patient samples and the use of tests to assess this neurocognitive domain.

With regard to visual memory, there is some evidence that BD-II patients could be impaired in this domain; however, it has been studied to a lesser extent in euthymic BD-II patients [48,54]. The meta-analysis conducted by Bora *et al.* showed that there are also small but significant differences in this domain when compared with the BD-I group, with more visual memory impairments in the latter [61]. However, among the studies that found visual memory impairment, only the study by Dittmann *et al.* assessed patients who fulfilled strict euthymia criteria [54].

EF & WM
WM may be considered a core deficit in BD-II disorder [60,61] since most of the studies have found a poorer performance in both BD-II euthymic patients and those in an interepisodic state compared with healthy controls [10,30,50,54,62,66]. In addition, when comparing BD-II patients with or without comorbid alcohol abuse/dependence, WM impairment was the only neurocognitive finding that was found in both groups compared with healthy controls [66]. Therefore, the authors concluded that this deficit was associated with the BD-II subtype. Although WM impairment is also present in BD-I patients, it has been suggested that WM could be a good predictor of psychosocial functioning specifically in BD-II, even after controlling for the effect of subsyndromal symptoms [10]. The TMT-B is a measure that is used to assess WM, as well as EF. Very few studies using this test in euthymic BD-II patients managed to detect impairment [50,54]. Although Torrent and colleagues did not find the TMT-B to be impaired in euthymic BD-II, a trend towards a poorer performance was detected in this group [10].

EF is a complex domain that encompasses a broad range of cognitive functions. To date, neither of the studies using the WCST, another test related to cognitive flexibility and set shifting, detected EF impairment in BD-II subjects [10,48,50,59]. Nevertheless, a meta-analysis pointed to a significant deficit for this measure [61]. As mentioned above, it should be taken into account that BD-II patients in the study conducted by Torrent *et al.*, although not being impaired, also showed a trend towards a worse performance when compared with healthy subjects [10]; additionally, the BD-II sample assessed by Savitz and colleagues was compared with relatives without a history of mental illness [48].

The interference measure from the Stroop Color-Word Test (SCWT), which is an inhibitory control measure, appeared impaired in all of the BD-II samples when compared with healthy controls [10,30,47,59]; however, only one of these studies rigorously assessed euthymic patients [10]. By contrast, in a functional MRI study focusing only on BD-II subjects, these patients did not differ in performance on the Go/No-Go task (which requires inhibitory control) when compared with healthy subjects. Both groups showed similar anterior cingulated cortex activity, although one might argue that this task was not sufficiently cognitively demanding [67].

Another neurocognitive process associated with EF is verbal fluency. With regard to phonemic verbal fluency, results from several studies suggest that it would be preserved in BD-II patients [10,30,47,48,50,51,59]. On the contrary, however, although few authors evaluated semantic verbal fluency in this bipolar subtype, findings point towards a lower performance in BD-II subjects when compared with healthy controls [10,30]. However, in their meta-analytic findings, Bora and colleagues pointed out that BD-I patients are more impaired in this domain, together with verbal memory [61]. In line with these data, it has been described that BD-I patients could have a more disorganized semantic structure compared with BD-II patients and healthy subjects, although BD-II patients also used less elaborate strategies of semantic memory organization than those of controls [51]. Hence, both bipolar groups used different patterns of semantic memory categorization. To the best of our knowledge, this is the first study providing qualitative differences in neurocognition between bipolar subtypes, rather than quantitative differences.

Overall, BD-II patients present some executive dysfunction, such as inhibitory control, as well as WM and semantic verbal fluency dysfunction, whereas other aspects related to EF (e.g., cognitive flexibility) need to be investigated in more detail. Some studies proposed that executive dysfunction may be more related to psychotic features instead of bipolar subtype [29,63]. Meanwhile, Andersson *et al.* suggested that deficits in EF in BD-II patients may be more related to psychomotor symptoms than to EF [47].

Attention & psychomotor speed

With regard to attention and psychomotor speed, it still remains unclear whether BD-II patients are impaired, since not all the studies found dysfunction in this neurocognitive domain. Despite some negative results, most of the studies found deficits in attention as assessed by different tests **(Table 1)** [10,47,49,50,54,62,68]. In some studies focusing on euthymic BD-II patients, these patients demonstrated poorer performance when compared with healthy subjects, whereas they were equally as impaired as BD-I patients [10,50]. Hence, the sustained attention deficit seems to be state-independent, and this fact reinforces the role of this characteristic as a potential endophenotype of the illness [68,69]. However, only one of the aforementioned studies used the Continuous Performance Test to assess the attention domain in euthymic patients [68]; this test has a high cognitive load, and it is more helpful for discriminating these kinds of deficits than other attention tests that imply lower rates of cognitive effort. Kung and colleagues also used this test, but their patients were in an interepisodic state [70].

Other neurocognitive domains

In the last few years, a growing interest has emerged in areas such as decision-making and social cognition. On the one hand, regarding decision-making, which is a critical issue for success in the social and vocational challenges of daily life, only two studies have addressed this issue in BD-II; both reports pointed out negative findings in BD, showing intact decision-making skills in unmedicated depressed as well as in euthymic subjects [46,50]. Instead, decision-making impairments appeared more related to patients with a history of suicide attempts, probably as a vulnerability risk factor to suicidal behavior [50]. On the other hand, some domains (e.g., social cognition and theory of mind [ToM]) have been scantly investigated in the BD-II subtype; only one recently published study has investigated this issue [71]. ToM is the ability to understand and predict other people's behavior by attributing independent mental states to them. ToM dysfunction has been found in remitted BD-I patients [72–74]; however, some studies have suggested that this deficit could be associated with attention and EF [72,73]. Similarly, Martino and colleagues detected that euthymic BD-I and BD-II patients had an impairment in ToM; however, this disturbance is mediated, at least partially, by attention/EF and exposure to psychotropic drugs [71]. In this study, social cognition measures were not independent predictors

of psychosocial functioning. Therefore, this is an area that should receive more attention in the future in order to clarify whether social cognition is a pure deficit in BD.

Less is known about the affective processing domain. Whereas one study found that only euthymic BD-I patients showed difficulties in facial emotion recognition [75], other researchers detected that both BD-I and BD-II patients had lower recognition of fearful facial expression than controls [71]. Another two studies showed that both bipolar groups demonstrated difficulties in affective recognition of some variety of positive emotions; however, it must be taken into account that most patients in these two studies were depressed [49,59].

■ **Cyclothymia, BD-NOS & SZA bipolar type**
To the best of our knowledge no previous studies have assessed neurocognition in cyclothymia or exclusively in BD-NOS. Some studies included BD-NOS patients; however, these were always in mixed samples. Therefore, given the lack of studies regarding neurocognition in these different entities, no summary statement can be made.

With regard to SZA, neurocognitive data of schizophrenia and SZA is usually mixed; that is, the majority of the studies focused on schizophrenia put these disorders together – many others compare SZA patients with schizophrenic patients. Furthermore, very few studies have focused on SZA bipolar type. Reichenberg *et al.* found that the SZA group was significantly impaired on verbal and visual memory, EF and attention/processing speed [7], and rates of impairment were also significantly higher in this group when compared with psychotic bipolar patients; 20–33% SZA patients were classified as neuropsychologically normal, whereas 42–64% of bipolar psychotic patients were classified as normal. Previously, these authors found that SZA patients showed premorbid neurocognitive deficits that were very similar to those of the future schizophrenic patients; they scored worse than future nonpsychotic BD patients [76]. In the same vein, Torrent and coauthors also found that SZA bipolar type patients showed more neurocognitive impairment than nonpsychotic bipolar subjects in several domains, especially with regard to verbal memory tests [10]. Recently, Studentkowski *et al.* also obtained similar neurocognitive data when comparing euthymic SZA patients with bipolar subjects [77]. Simonsen *et al.* found that all groups who

presented with a history of psychosis (such as schizophrenia, SZA and BD) had a similar neurocognitive impairment, whereas no differences were detected between the bipolar group without lifetime psychotic symptoms and normal controls [63]. Thus, several researchers suggest that there may be a continuum between schizophrenia, SZA and BDs [10,63,78,79]. Vieta has suggested that it is necessary to develop an individualized treatment plan for SZA bipolar type patients, from pharmacotherapy to psychoeducation, in order to achieve the best possible outcomes [80].

Discussion
Neurocognitive impairment constitutes a core feature of bipolar illness that includes problems in speed of processing, attention/vigilance, WM, verbal/visual learning and memory, reasoning and problem solving and social cognition, and can be detected across BD-I and BD-II subtypes. Meanwhile, no study has been specifically focused on cylcothymia or on BD-NOS; thus, more research is needed in order to ascertain whether these entities are associated with neurocognitive disturbances. Overall, the main neurocognitive deficits in BD are attention, memory and EF [39,69,81,82]. The majority of studies have been conducted in the BD-I subtype; however, in most of these studies patients were in acute episodes, with subsyndromal symptomatology or the period of euthymia not being long enough. The same occurs in the BD-II subtype. This review has given priority to samples with euthymic patients. Although neurocognitive dysfunctions appear in overall BD, some meta-analytic findings point out that BD-I patients may present greater deficits in some neurocognitive domains, such as verbal memory and semantic verbal fluency [61]. This may suggest neurobiological differences between the two subgroups, which will be helpful in order to determine neurocognitive endophenotypes in BD subtypes [30,60]. Differences between BD-I and BD-II groups might be explained more by differences in magnitude rather than different neuropsychological profiles. In this respect, BD-I patients may be more impaired due to the manic episodes, which are known to be neurotoxic, or due to secondary features, such as psychoses, age of illness onset or treatment [61]. Similarly, a recent study highlighted that manic recurrences may incur a long-term neuropsychological impact [42].

In this regard, the literature has revealed other critical factors that can influence neurocognition

in BD, such as age, premorbid IQ, education, course of illness or chronicity factors, mood state, substance use and adverse effects of medications [23]. Other important factors, as mentioned above, may be history of psychosis or prevalence of subthreshold depressive symptoms [83]. Furthermore, it is worth mentioning that the role of pharmacological treatments upon neurocognition is a complex issue [84]. On the one hand, medication carries its own cognitive side effects. On the other hand, the neuroprotective effects of some treatments such as lithium have been described. In this regard, data from a recent meta-analysis suggest that lithium appears to have only a few minor negative effects on neurocognition [85]. However, we cannot rule out the effects of medications since most bipolar patients are polymedicated and at different dosages, which makes the analysis of pharmacological treatment difficult. Moreover, neurocognitive disturbance has been detected in the onset of the illness, as well as in unaffected relatives [44,81,82]. Another important factor that seems to influence neurocognition is comorbid substance abuse, which seems to pose an extra cognitive burden [83].

With regard to neuroanatomical differences, recent neuroimaging studies support the idea that the two bipolar subtypes may have different neurobiological characteristics [86], which is consistent with some differences for certain neurocognitive deficits between subtypes. It has been revealed that dorsal and posterior neocortical gray matter regions and the medial temporal region may be more abnormal in BD-I than in BD-II [86]. These findings could be related to the greater verbal memory and executive deficits detected in the BD-I group in several studies [10,30,57,62]. Liu *et al.* also found distinct neuropathological substrates in white matter (by fractional anisotropy) between BD-I and BD-II subjects [87]. To the best of our knowledge, only one study has focused on functional neuroimaging in BD-II [67]. Therefore, further investigations analyzing cerebral activation are needed in order to clarify the differences between bipolar subtypes. Moreover, future research also needs to control for mood states, since neither of the studies comparing BD-I and BD-II were conducted with euthymic patients. For instance, another study analyzing MRI-measured white matter lesions did not differentiate between euthymic BD patients with neurocognitive impairment and healthy controls [88].

The presence of enduring neurocognitive deficits may have several implications at the level of functioning. As shown above, several authors have demonstrated an association between neurocognitive impairment and a lower functional outcome. These difficulties in several domains of the everyday lives of patients (e.g., a marked functional deterioration in their interpersonal relationships [89]) may involve lower self-esteem [90,91]. Since neurocognitive measures have been shown to predict long-term functional outcome, these should be considered to be therapeutic targets. Novel neuropsychological interventions, such as cognitive remediation (CR), may be useful in order to improve neurocognition, as well as to achieve functional recovery in BD patients. To the best of our knowledge, only one study has been conducted that specifically focused on this issue in BD patients, with encouraging findings [97]; therefore, more replication in this field is necessary and, as is clearly seen from this review, interventions could be adapted to take into consideration the bipolar spectrum characteristics. For future research, CR should involve tasks that include real situations that the patients will have to manage in every day of their lives. This aspect could help to decrease anxiety and insecurity and enhance the self-esteem of patients.

In conclusion, multiple factors could be involved in the neurocognitive impairment in BD; however, it is very important to establish the euthymia criteria and residual symptoms that should be controlled. Furthermore, the combination of psychoeducation therapy and neurocognitive remediation could improve awareness of illness, treatment adherence, prevention of future relapses and reduction of cognitive deficits, which would improve functional outcome and generate neuronal plasticity in BD.

Future perspective: from CR to functional remediation

During the last few years, several studies have demonstrated a relationship between low psychosocial outcome and neurocognitive dysfunction, mainly verbal memory impairment and some measures related to EF and attention [10,33,37,57,92–94]. These findings are useful for developing new psychosocial interventions (e.g., CR) targeted at enhancing not only neurocognitive deficits, but also the associated psychosocial impairments in these patients. Different approaches to rehabilitation

treatments conducted with the aim of improving cognitive function have been successfully developed in the field of schizophrenia [95,96]. Previous advances and experiences in this area may be helpful in implementing new neurocognitive treatments in BD. In this regard, few studies have focused on affective disorders. The vast majority of the research has been conducted with heterogeneous samples, and only one of these studies was specifically focused on BD [97]. These authors explored a new CR treatment for improving not only neurocognitive deficits, but also residual depressive symptoms, in an attempt to improve occupational and overall functioning. It has already been confirmed in several studies that subdepressive symptomatology is another factor contributing to psychosocial dysfunction [94,98–101]. The authors suggested that an improvement in EF may be related to improvements in occupational functioning. Although the results of this study are encouraging, it is still is too early to draw any conclusions, and further research needs to be carried out in order to assess any potential benefits regarding the implementation of these programs in BD patients. In this regard, Martinez-Aran *et al.* have coined the term 'functional remediation' to define a strategy aimed at targeting the critical factors for full psychosocial adjustment [102]. In the next few years, this intervention will probably involve neurocognitive techniques, but also psychoeducation on cognition-related issues and problem-solving within an ecological framework aimed at achieving a functional recovery. Results of future research may eventually show the potential benefits of functional remediation.

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