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REVIEW

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Neurocognitive Impairment Across the Bipolar Spectrum

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SUMMARY

Bipolar disorder is a severe mental illness that affects nearly 4.4% of the general population when bipolar spectrum disorders are taken into account. Neurocognitive impairment is thought to be a core deficit of this illness since it is present during euthymia. In fact, 40–60% of euthymic patients present with neurocognitive disturbances. Not only the clinical factors but also disturbances in neurocognition can influence the functional outcome of BD patients. Hence, further research is needed in order to clarify the relationship between these variables. Despite the growing body of evidence that has emerged during the last decade, no unique neurocognitive profile has been proposed yet for either BD subtype. The majority of the studies recluted heterogeneous samples (including both bipolar I and II) or focused on BD-I patients only. The aim of this review is to give an overall picture of the main neurocognitive disturbances found in the bipolar spectrum and particularly in BD-II, where the findings are more ambiguous. An extensive review of all the literature has been done regarding this subtype (from 1980 until July 2009). Data available until now suggest that deficits are present across the bipolar spectrum (BD-I and BD-II), but they seem slightly more severe in BD-I. The extent to which either subtype share—or not—some similarities is still unknown. More studies are required but it would also be interesting to reach a consensus in the neuropsychological assessment of BD to facilitate comparisons between the different studies.

Neurocognitive Impairment in Bipolar Disorder and its Implications on Functional Outcome

Bipolar Disorder (BD) is a chronic and recurrent mental illness that causes unusual mood shifts. When the whole bipolar spectrum is considered, it affects nearly 4.4% of the general population [1] and the World Health Organization (WHO) ranks BD as the seventh leading cause of years lost due to disability in males, the eighth in females [2].

During the past decade, a growing body of evidence suggests that patients suffering from BD present cognitive disturbances. These impairments are likely to be independent of affective states, since they remain even during long-lasting euthymia [3–5]. Hence, Kraepelin was partially wrong and cognitive decline is not only present in schizophrenia but also in BD. In fact, an interesting study conducted in Argentina [6], reported that 40–62% of bipolar euthymic patients show some sort of impairment (from 1 to 5 affected cognitive domains). When assessing psychosocial dysfunction, one study [7] found similar prevalence to that seen in cognitive impairment. Specifically, it was reported that 30–60% patients failed to achieve functional recovery (measured by impairment in employment and social functioning). These similarities in prevalence may not be just a mere coincidence; actually, it may suggest that both cognitive dysfunction and functional outcome are somehow linked. Cognitive impairment may affect everyday activities, patient's ability to work and a delay reemployment; therefore, there is a growing need to elucidate not only the neurocognitive impairment, but also its implication on functional outcome, as outlined in a recent review [8]. Neurocognition clearly has an important role in functional outcomes of bipolar patients [9].

Despite the efforts in these years, no specific cognitive profile for the different bipolar subtypes (type I, type II, cyclothymia and bipolar not-otherwise-specified, BD-NOS) has been clearly delineated. Moreover, when compared with schizophrenia or unipolar depression (UP), BD does not present a specific distinguishing pattern. The most studied BD subtype is bipolar I followed, to a lesser extent, by bipolar II; however, in some studies both subtypes are not specified [10,11]. That may be one of the reasons why it is not known to what extent bipolar I and bipolar II present similarities regarding the neurocognitive profile. In this review, we provide an outlook of the recent literature focusing both on bipolar I and bipolar II disorder, but especially in the latter, which is the least studied.

Neurocognitive Impairment in BD-I Subtype

Verbal memory [12–19] executive functions [4,12,19–23] and attention [4,21,22,24,25] are the cognitive domains most frequently reported as affected in euthymic bipolar I patients.

When compared with schizophrenia, BD-I appears to present smaller magnitudes of neurocognitive impairment [26,27], even at the first episode of the illness [28]. Therefore, the difference is quantitative rather than qualitative [29]. This divergence may be explained by different reasons. On one hand, the neurodevelopmental hypothesis states that schizophrenic patients show cognitive impairment even before the onset of illness and the decline might continue even thereafter. In fact, some studies have reported differences in premorbid IQ between patients with schizophrenia and bipolar disorder, with the latter group showing higher scores [30,31]. However, in bipolar disorder the current perspective is quite different: while some studies suggest a genetic liability for this illness [32,33], the data collected until now does not allow to conclude that this disorder fits in the neurodevelopmental hypothesis [34]. Moreover, the scarcity of follow-up studies [12,35–37] does not permit to state whether these impairments in the bipolar cohorts are static or progressive.

On the other hand, the continuum model of psychosis proposes that it there may be a nosological continuum between psychotic and nonpsychotic subtypes of bipolar disorder and that cognitive impairment is determined more by history of psychosis than by a diagnostic subtype supporting a dimensional approach rather than a categorical one. There is some evidence supporting this theory both in schizophrenia and bipolar disorder [16,33,38,39].

Another important issue is that the functional outcome relies somehow on the neurocognitive processes. It is well established that neurocognition influence the functional outcome in bipolar patients and it has been reported both in cross-sectional studies [3,4,40,41] and follow-up studies [35,42–45]. So that, there is a need to further investigate the directionality of this relationship and to find out whether one is the cause of the other or whether they occur concomitantly.

To conclude, cognitive impairment in BD-I seem to be trait-like deficits with persistent functional implications. However, the specific pattern of these neurocognitive disturbances has not been defined yet and it is likely that no pathognomonic pattern will ever be identified. Because BD shares both environmental and genetic risk factors with other disorders (e.g., bipolar II disorder, schizophrenia, schizoaffective disorder, unipolar depression...), more follow-up studies should be conducted in the near future, not only ones assessing neurocognition, but also those evaluating the functional outcome. Studies with first-episode patients and individuals with high risk for psychosis could also help to elucidate the nature of neurocognitive impairment in BD-I. The role of medication is also important and represents a real challenge, because the effects of medication may change across the different spectrum subtypes and conditions, and medication effects are not well understood as yet [46]. On the other hand, repeated manic episodes may probably have a negative impact on the neurocognitive performance of BD-I [47,48].

Neurocognitive Impairment in BD-II Subtype

In the past years several reviews supporting recognition of BD-II as a distinct category within mood disorders have been published [49]. However, the specific neurocognitive status of BD-II still remains unclear. Only few studies have focused on neurocognitive impairment in BD-II, probably due to the fact that it is an underdiagnosed subtype.

With regard to general intellectual function, most of the studies have not found significant differences between BD-II and healthy subjects neither in the estimated current intelligence quotient (IQ) nor the premorbid IQ [17,50–54]. Only one study found that both BD-I and BD-II patients groups differed significantly from the healthy controls as to premorbid IQ, but they did not differ significantly one from another [55]. Only two reports have considered an index of IQ change in order to assess intellectual decline and found that BD-II patients scored significantly lower than BD-I on it [56,57]. The authors suggested that persistent depression, rather than mania, may represent a key pathophysiological factor with a higher risk of developing cognitive abnormalities.

With regard to attention and psychomotor speed in BD-II patients, the results are contradictory, some authors found significant differences in attention and psychomotor speed, while others have not, probably due in part to the disparity in attentional measures used. Only one study that assessed attention by the means of the Continuous Performance Test did not detect deficits in BD-II patients [58]. However, the same authors found deficits in attention and psychomotor speed assessed with other tests. In some studies, euthymic BD-II patients were found to perform poorer when compared to healthy controls [50,55]. An interesting study that compared depressed unmedicated BD-II patients and depressed medicated BD-II patients, found that the latter group performed poorer than the former in sustained attention. These differences may be explained by treatment with mood-stabilizing agents [54]. Surprisingly the authors did not find attentional deficit in unmedicated BD-II subjects.

On one hand, two studies did not find impaired attention using the digits forward [17,51], on the other hand, three reports did not find impairment in psychomotor speed using the TMT-A [56,58,59]. Despite these negative results, most of the studies found deficits in attention either using one test or other.

With regard to learning and verbal memory, several studies found impairment in BD-II patients [3,50,53,56] and in two of them BD-II patients had an intermediate level between the BD-I and the healthy group [3,50]. It is noteworthy that only the study conducted by Torrent et al. [50] assessed patients with restrictive euthymia criteria. On the contrary, Summers et al. [56] found that BD-II patients were more impaired in verbal memory measures that those with BD-I. However, the small sample size of BD-II in this study should be taken into account as it could have lead to type-II errors.

Five studies failed to find deficits in verbal memory in BD-II [17,51,55,58,59], whereas in most of them a significantly worse performance in BD-I patients was observed [17,51,55,59]. As mentioned before, the continuum model of psychosis states that neurocognitive dysfunction depends more on history of psychosis

than on diagnostic subtype. A study conducted in Norway [39] found that diagnostic subtype only had significant main effects on two verbal recall measures, while history of psychosis had significant main effects on all subscores.

Discrepancies between studies do not allow drawing conclusive results; however, it might be mild-moderate verbal memory impairment between BD-I and healthy controls, since four out of nine studies detected poorer performance in verbal memory in BD-II patients.

With regard to visual memory, most of the studies did not report impairment in this domain [51,52,54,58,59]. However, three studies detected deficits in visual memory [53,55,56]. Therefore, the visual memory disturbance, if confirmed, it would be relatively small. It may depend on factors such as mild depressive symptoms or prior history of psychotic symptoms.

Considering working memory, most data indicate that there is a deficit in euthymic BD-II patients, as well as in subjects with subsyndromal symptomatology [17,50,53,55,56,59]. Only three reports did not detect any deficit in this domain [51,52,54]. It is likely that deficits in this area may be one of the core features of cognitive dysfunction in BD-II.

Executive functions also encompass phonemic verbal fluency, which seems to be preserved in BD-II subjects [17,50,51,53,56]. Only Harkavy-Friedman et al. [58] found impaired phonemic verbal task but this dysfunction may represents a state-dependent characteristic of depression [47,60], since all patients in Harkavy-Friedman's study were depressed. Fewer studies assessed semantic verbal fluency, only two out of three found a deficit in this area [17,50].

The Wisconsin Card Sorting Test (WCST), the Intra-Dimensional/Extra Dimensional Set-Shift subtest (IDED), and the Trail Making Test (TMT-B) are tests to assess cognitive flexibility. In studies using the WCST, BD-II patients were preserved [50,51,56]. Only one out of two studies using the IDED found that BD-II patients scored significantly lower than BD-I [56]. In a study conducted by our group [50], although no significant differences were found in the WCST and the TMT-B, a trend towards a poorer performance was detected in BD-II patients. Only Dittmann et al. [55] detected impaired TMT-B in this subtype.

Interestingly, all the studies using the Stroop Color-Word Test, which assesses interference, reported impaired inhibitory control in BD-II patients [17,50,53,56].

Overall, it might be a decrease of executive functions in BD-II subjects, although it appears to be more evident in BD with psychotic features (regardless type I or II) [39].

Other cognitive functions that deserve more research in the field of BD-II neurocognition are motor functioning, affective processing, decision-making, and social cognition. Little is known in these domains. Harkavy-Friedman et al. [58] detected a significant poorer performance on a simple motor task in depressed BD-II subjects. Instead, Berns et al. [61] failed to find differences in reaction time between euthymic BD-II patients and healthy controls, but they showed different brain responses. Recently some authors have suggested that motor speed seems to be suitable endophenocognitype for schizophrenia and bipolar disorder [62].

Regarding affective processing Derntl et al. [63] observed a reduced emotion recognition performance in BD-I but not in BD-II patients. On the other hand, other authors [54,56] reported biased in affective processing in depressed subjects with BD-II in the recognition of different types of emotions, although these alterations might be a depression-related cognitive deficit.

Whereas social cognition and theory of mind (ToM) is a neglected domain specifically addressed to BD-II subtype, several studies conducted with BD-I remitted patients showed that ToM deficits persist beyond acute mood episodes [64–66]. Nevertheless, it is necessary to clarify the relationship between ToM with other cognitive functions since some studies have demonstrated an association with executive function and attention [64,65].

Prior research has shown that both manic and depressive patients had impairments in decision-making, however, studies remain controversial regarding euthymic patients [67,68]. It is possible that lower performance in decision-making might represent a vulnerability factor to suicidal behavior [69]. Concerning BD-II patients, only one study has assessed specifically the decision-making performance of these patients [52], showing an intact performance, however all the patients were unmedicated depressed subjects, limiting generalizability of the findings, and the sample size was relatively small. Therefore, it should be necessary to assess this issue in euthymic BD-II patients.

All these studies with BD-II patients could be classified into four research lines. The first one would comprise just one study [55], which concludes that there are no essential differences in neuropsychological profiles between BD-I and BD-II patients, suggesting a similar pattern of cognitive deficits.

The second one includes other studies in which BD-II present an intermediate performance between BD-I and the healthy group, specifically in verbal memory [3,50] and executive functions [50]. Similarly, some authors suggest that BD-I patients have more widespread cognitive dysfunction than BD-II group [17,59].

The third group comprises two studies. They report that cognitive deficits could be more severe and pervasive in BD-II than BD-I patients [56,58]. As mentioned before, it is suggested that recurrent depressive episodes may have a detrimental and long-lasting effect on cognition.

Finally, the fourth group consists of two studies [51,52]. Neither one detected deficits in BD-II; however, the relatively small sample size in these studies must be taken into account and therefore the likelihood of type-two error increases.

Anderson's study [53] may deserve special mention since is the only one that compares uniquely BD-II versus healthy controls. It is difficult to classify it into one of the above-mentioned proposed groups since the authors discuss the functional significance of the cognitive impairment (which is widespread, except for the phonemic verbal fluency). They suggest that the disturbances regarding executive function may be related to psychomotor speed, and not primarily to dysexecutive functioning.

For a general overview of the positive and negative findings, see Table 1.

While in BD-I one of the crucial factors was the history of psychosis, in BD-II, where psychosis is not so common [70], a major player in the findings may be the existence of subthreshold depressive symptoms, which are generally more frequent in BD-II than in BD-I and should be controlled for [49].

Table 1 General findings for the most important neurocognitive domains involved in BD-II

	Verbal Memory and Learning	Working memory and/or other Executive Functions	Attention and/or psychomotor speed	Visual Memory	Emotional Processing
Positive Findings	Martínez-Arán et al., 2004 [47]; Summers et al., 2006 [56]; Torrent et al., 2006 [50]; Andersson et al., 2008 [53]	Andersson et al., 2008 [53]; Dittmann et al., 2008 [55]; Summers et al., 2006 [56]; Simonsen et al. 2008 [17]; Torrent et al., 2006 [56]; Hsiao et al., 2009 [59]; Harkavy-Friedman et al., 2006 [58]	Hsiao et al., 2009 [59]; Andersson et al., 2008 [53]; Harkavy-Friedman et al., 2006 [58]; Torrent et al., 2006 [50]; Holmes et al., 2008 [54], only in medicated patients; Dittmann et al., 2008 [55,56]	Andersson et al., 2008 [53]; Summers et al., 2006 [56]; Dittmann et al., 2008 [55]	Holmes et al. 2008 [54], only in medicated patients; Summers et al., 2006 [56]
Negative Findings	Dittmann et al., 2008 [55]; Harkavy-Friedman et al., 2006 [58]; Hsiao et al., 2009 [59]; Simonsen et al., 2008 [17]; Savitz et al., 2008 [51].	Savitz et al., 2008 [51]; Taylor-Tavares et al., 2007 [52]	Savitz et al., 2008 [51]; Simonsen et al., 2008 [17]	Hsiao et al., 2009 [59]; Harkavy-Friedman et al., 2006 [58]; Taylor-Tavares et al., 2007 [52]; Savitz et al., 2008 [51]; Holmes et al., 2008 [54]	Derntl et al., 2009 [63]

Note: A study was classified as positive when differences were found between BD-II patients and the comparative group. When no differences were found between groups, the study was classified as negative.

As far as we know, just one study measured the impact of neurocognitive disturbances on functional outcome in BD-II [50]. It was found that a measure of executive dysfunction constituted a good predictor of psychosocial functioning. This relationship deserves further investigation since a recent study [71] detected that BD-II euthymic patients are as disabled as their counterparts (BD-I) in functional outcome. The role of neurocognitive impairment on functional outcome of BD-II seems to be an unresolved matter and very few researchers [50] have focused on this issue.

To conclude this section, BD and UP may share some similarities with regard to neurocognitive impairment, especially some disturbances in verbal memory and executive functions. However, these dysfunctions in UP appear to be broad and unselective, like in BD. Therefore, to date, it is very difficult to ascertain whether BD is different from UP in terms of neurocognitive profile. More comparative studies are needed in order to find out any possible detail that identifies a neurocognitive pattern as unique for each disorder, and the influence of different medication regimens should be controlled for.

A Brief Overview: BD versus UP

Some studies with Unipolar (UP) euthymic patients also suggest the existence of a core cognitive dysfunction independently of psychopathological status in this disorder [72–74]. Some studies report nonspecific and widespread deficits [75,76] while others found specific impairment. For instances, Bhardwaj et al. [74] found neurocognitive impairment when assessing executive functions (assessed with the WCST) in a sample of euthymic patients with recurrent depression. Neu et al. [77] reported deficits in verbal memory and verbal fluency after the treatment and at least 6 months of euthymia.

A recent interesting study [78] compared neurocognitive impairment in bipolar versus unipolar depressed patients. The findings suggest that disturbances in sustained attention appear to be specific to bipolar disorder euthymic patients. But, when bipolar depressed patients and unipolar depressed patients are compared, executive dysfunctions are present in both groups, suggesting that the impairment in this area is likely to be a marker of depression. It would have been interesting to include another group, comprised of unipolar remitted patients, in order to compare the performance with the bipolar euthymic group.

Discussion

There is some indication that neurocognitive impairments can be detected across all the entities within the bipolar spectrum.

When comparing deficits across conditions, the scarcity of studies, especially those with BD-II patients, makes difficult an unambiguous interpretation of the results; albeit it appears that there are subtle differences between BD-I and BD-II regarding cognition. Except for two studies [51,52], all of them detected cognitive deficits in BD-II, mainly in the areas of attention/psychomotor speed, working memory, inhibitory control and, to a lesser extent in verbal memory. Underlying mechanisms for differences in cognitive functioning between the two diagnostic subtypes could be partially due to genetic liability [55] and these may indicate neurobiological differences [17]. Differentiation in cognitive profiles in both subtypes could lead to better identification of cognitive endophenotypes in BD. Nevertheless, to our knowledge, no studies assessing neurocognitive performance in cyclothymia or BD-NOS are available; therefore, speculation can only be made in this field, for instances, if we assume a continuum model of neurocognitive impairment, it might be expected that cyclothymia would show milder cognitive deficits along this continuum. With regard to

BD-NOS, it is not common to include them in studies when assessing neurocognition, therefore, studies ad-hoc should be designed in order to clarify whether both diagnostic subtypes are impaired or not.

We may say that the ambiguous findings, especially those reported in BD-II, reflect differences in methodology of the studies; first, some studies include small sample size or use different comparative groups in different mood states of the illness making it difficult to draw clear conclusions. Second, the heterogeneity of the sample is not a trivial issue: illness duration, number of episodes, previous rapid cycling, severity of episodes, among the rest, can influence the neuropsychological performance [3,11,47], as well as the functional outcome [79]. Perhaps the most critical factors when comparing cognition across the bipolar spectrum are history of psychosis, prevalence of subthreshold depressive symptoms, and the role of medication [80]. Moreover, we cannot rule out the impact of repeated episodes on the cycle of cognitive impairment in these patients [81,82]. Third, it would also be important to standardize the methodology of studies assessing the neuropsychological performance. It is necessary to reach a consensus when assessing neurocognition in BD in order to facilitate comparison between different studies. Recently, a committee including expert researchers in BD, have proposed a compendium of tests, which could be the first step in standardizing a comprehensive neuropsychological assessment [83].

Other methodological considerations could be establishing a clear definition of euthymia criteria because it is known that symptomatology, even at subsyndromal levels, can influence the neuropsychological performance [24,84]. The role of medication is also an important issue [80]. Since BD-I and BD-II do not share the same treatments these may exert different effects upon neurocognition. However, more studies on this subject need to be developed. Nowadays, medication in BD is considered to be like a two-edged sword, because in one hand it targets mood symptomatology, but on the other hand it carries its own cognitive side-effects [46]. Finally, it would be useful to conduct specific studies, which separate the bipolar subtypes because it can not be assumed that the course and evolution are the same for each subtype (BD-I; BD-II; BD-NOS; Cyclothymia).

Data available until now allow us to cautiously conclude that neurocognitive impairment in BD spectrum seems to be neither selective nor specific. This may be a very generic conclusion but little can be said since neurocognitive processes relies on a network of multiple neural interconnections. Therefore, it is difficult to interpret these contradictory results as isolated indicators of any cerebral region. For instances, Ferrier et al. [85] found deficits in the executive control of working memory in a sample of euthymic patients with BD. They suggested that the findings may reflect frontal lobe damage or disruption of frontosubcortical or mesolimbic circuitry. Similarly, another study [11] comparing mild-depressed UP patients versus BD patients found a similar deficit profile across learning and memory functions. The authors interpreted the results as an implication of medial temporal systems, which could be common to both disorders (UP and BD). Hence, it is still a challenge to disentangle the role of every single variable that causes neuropsychological impairment in psychiatric disorders.

In conclusion, data on the "lower" end of the bipolar spectrum are urgently needed, but the findings so far concerning BD-II as compared to BD-I suggest that BD-II is not free of cognitive impairment, and that the functional impact of cognitive disturbances may be as high as that found in BD-I. Therapeutic implications may derive from these findings, suggesting that pharmacological and nonpharmacological interventions should be adapted taking into consideration the bipolar spectrum characteristics.

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Conflicts of Interest

Professor Eduard Vieta has served as consultant, advisor or speaker for the following companies: Almirall, AstraZeneca, Bial, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck and Co. Inc., Novartis, Organon, Otsuka, Pfizer Inc, Sanofi-Aventis, Servier, Shering-Plough, Takeda, United Biosource Corporation, and Wyeth. Dr. Martinez-Aran has received research funding from the Spanish Ministry of Innovation. Dr Rafael Tabarés-Seisdedos has received grants from Lilly, Pfizer, and Astra-Zeneca Companies.

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