The predictive significance of neurocognitive factors for functional outcome in bipolar disorder

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Purpose of review
Poor psychosocial functioning in bipolar disorder often persists even after affective symptom remission. Cognitive deficits, which have emerged as a core feature of bipolar disorder in the past few years, are among the factors implicated in adverse psychosocial outcomes of patients suffering from bipolar disorder. This review aims to overview recent literature on the association of neurocognition and psychosocial functioning in bipolar disorder.

Recent findings
Cognitive deficits (mainly general neurocognitive functioning, attention and verbal learning and memory) are important determinants of poor psychosocial functioning in bipolar disorder, although to a lesser extent than in schizophrenia. Although affective symptoms appear to be a more important predictor of functional outcome in symptomatic patients, cognitive deficits also play a significant role, more readily recognizable in euthymic or chronic patients.

Summary
Given the importance of cognitive impairments for psychosocial outcomes in bipolar disorder, the development of interventions targeting cognitive impairments is imperative for improving recovery rates and quality of life in patients, even after adequate symptom control.

Keywords
bipolar disorder, functional outcome, neuropsychology, psychosocial outcome

INTRODUCTION

As early as 1904, Kraepelin [1] had observed that, when manic-depressive insanity 'has lasted for some time and the attacks have been frequently repeated', a decline in social and professional functioning followed, associated with residual symptoms such as 'a certain constraint and a lack of initiative, depressed shy behavior, slight lassitude and great need of sleep' [2]. He did not link this poor functional outcome to cognitive deficits, though, in his view, manic-depressive insanity, unlike dementia praecox, never led to profound dementia [2].

Poor premorbid functioning indeed tends to present early in the course of bipolar disorder. Although many patients with bipolar disorder regain psychosocial functioning upon symptomatic remission, the majority of patients suffer significant and persistent interpersonal, social and vocational impairment, often despite adequate control of affective symptoms [3,4]. Understanding the factors associated with functional disability in bipolar disorder is of primary importance for developing interventions that might improve functional recovery and quality of life in patients.

Various factors have been implicated in adverse psychosocial outcomes in patients with bipolar disorder, such as genetic factors, illness severity including residual symptoms, comorbid substance use, psychotic symptoms and anxiety, and cognitive deficits [4]. The latter are of particular interest, as they have emerged as a core feature of bipolar disorder in the past few years, even after symptom remission [5▪]. Four recent meta-analytic studies

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KEY POINTS

- Neurocognitive deficits significantly predict functional impairment in bipolar disorder, although less so than in schizophrenia.
- General intellectual capacity, attention and verbal memory appear to be the strongest predictors of functional outcome.
- Depressive symptoms possibly affect psychosocial outcomes more strongly than neuropsychological deficits.

of cognitive performance in euthymic patients with bipolar disorder have reported medium to large impairments in patients compared with healthy controls in a range of neuropsychological domains such as attention/vigilance, processing speed, response inhibition, and set shifting, as well as verbal and visual learning and memory [6–9]. Moreover, these deficits appear to be present, although in a lesser form, in first-degree relatives of patients [6,7], indicating that cognitive dysfunctions might be a trait characteristic of bipolar disorder. Accordingly, the number of studies that investigate the association of neurocognition and psychosocial functioning has been steadily increasing in the past years. The aim of the present review was to provide an integrative overview of most recent findings in this field of research. To this end, articles written in English and published between January 2010 and June 2012 were identified through searches in two major literature databases (*PubMed*, *ISI Web of Knowledge*) and through additional manual screening of the literature sections of retrieved studies.

NEUROCOGNITIVE CAPACITY AS PREDICTOR OF FUNCTIONAL OUTCOME IN BIPOLAR DISORDER

Quite a number of studies [10▪▪,11▪▪,12▪,13▪,14▪▪, 15▪,16▪▪,17▪,18▪,19▪▪–21▪▪] have investigated the association of neuropsychological performance with various measures of functional outcome in bipolar disorder in the past 2 years. Of those, three large studies, which have either clustered neuropsychological variables together in the statistical analyses (Simonsen *et al.* [16▪▪], $n = 56$ patients with nonpsychotic bipolar disorder I) or used a composite neuropsychological variable (Bowie *et al.* [11▪▪], $n = 130$ patients with bipolar disorder I; Depp *et al.* [18▪], $n = 134$ patients with bipolar disorder I), found that cognitive deficits significantly predicted social outcome [11▪▪,16▪▪,18▪] and functional status [11▪▪,16▪▪]. Only one study [19▪▪] found no association between neurocognition and a self-report measure of social functioning in a sample of 106 patients with bipolar disorder I.

Among the studies that differentially investigated the impact of specific cognitive deficits on functional outcome, the vast majority have revealed a relationship of some sort. However, the exact patterns of association vary; for example, Martino *et al.* [14▪▪] found significant associations of functional capacity with measures of attention (Digit Span Forward, Trail Making Test A) and executive functions (Trail Making Test B, Verbal Fluency) in a sample of 48 euthymic patients with bipolar disorder I. On the contrary, in a large study by Jabben *et al.* [13▪] that included a mixed sample of 74 patients with bipolar disorder I and II, the only neuropsychological function associated with functional outcome was reaction time on a selective attention task. Attention, measured with an ecologically valid task, was also associated with the probability of being employed in another study [15▪], which included 29 euthymic patients with bipolar disorder. In contrast, in a study that cross-sectionally investigated the influence of cognitive impairments on psychosocial outcome in 33 patients with bipolar disorder 15 years after an index manic episode, significant predictors of outcome were processing speed (for global function and social adaptation) and verbal learning and memory (for occupational status). Verbal memory at baseline was also a significant predictor of overall outcome in the two longitudinal studies in this group [10▪▪,21▪▪]: Bonnin *et al.* [10▪▪] investigated the neurocognitive variables that would best predict functional outcome in 32 euthymic patients with bipolar disorder I and II after an average of 4 years; in that study, occupational functioning was predicted by working memory at baseline. Also, in a study that included 53 participants with a recent diagnosis of a first manic episode, baseline verbal memory was the only significant predictor of independent functioning 6 months after the episode [21▪▪]. Another study conducted in 41 euthymic patients with bipolar disorder I [20▪▪] also found various cognitive variables including executive functions, memory and verbal memory were significantly correlated with global functioning. However, in a multiple linear regression analysis full-scale IQ was the only significant cognitive predictor of global functioning. The authors of this study point out that, since most neuropsychological variables are significantly intercorrelated, findings regarding neuropsychological performance in patients might reflect general cognitive ability rather than domain-specific performance.

There is only one exception to the above pattern of significant associations between cognition and

functional outcome: in a study by Wingo *et al.* [17▪], the probability of social functional recovery measured with a self-report scale was not associated with any neuropsychological measure in a sample of 65 patients with bipolar disorder I and II. However, the definition of recovery in that study relied on subjective recall, which might have affected the findings, given that 25% of patients were depressed at the time of assessment.

The occurrence of significant associations across a number of studies investigating patients with bipolar disorder in various stages of their illness and using different outcome measures (self-rated vs. observer-rated scales, general functional capacity vs. specific function domains) renders credibility to the notion of neuropsychological deficits as significant predictors of functional outcome in bipolar disorder. Attention and verbal memory appear to be the most plausible candidate neuropsychological functions involved, although general cognitive capacity might be of equal or even greater importance (see [20▪▪]). However, methodological limitations preclude more specific inferences. First of all, most studies suffer from relatively small sample sizes; this limits the interpretability of statistical analyses, which usually involve a great number of neuropsychological and clinical variables. Second, certain limitations need to be considered when using measures of functional outcome. For example, self-report measures have questionable validity and might be affected by mood state [11▪▪,22,23], and the use of categorical milestones such as employment and independent living may be influenced by contextual factors such as societal support, availability of jobs, ethnicity, and disability compensation legislation [11▪▪,24]; moreover, self-rated and observer-rated measures of functional outcome do not overlap completely (e.g. [16▪▪]), and various measures of outcome might have different determinants (as was the case in [10▪▪]). Therefore, the use of multiple measures of functional outcome might be advantageous in future studies. Finally, there is a definite lack of longitudinal studies (with the exception of two studies by Bonnin *et al.* [10▪▪] and Torres *et al.* [21▪▪]), and no study has so far assessed the longitudinal evolution of cognitive and psychosocial functioning over time and their associations.

COMPARISONS WITH SCHIZOPHRENIA

The cognitive differences between schizophrenia and bipolar disorder have been suggested to be quantitative rather than qualitative in nature [25,26] and, in fact, these differences do not appear to be sufficiently large to differentiate the two disorders [27]. As a result, the dichotomization of severe mental disorders into schizophrenia and bipolar disorder has been questioned and a more dimensional approach has been proposed. In this regard, studies comparing the contribution of neuropsychological deficits to functional outcome in bipolar disorder compared with schizophrenia are of particular interest.

Four large studies have investigated predictors of functional outcome comparatively in schizophrenia and bipolar disorder. Bowie *et al.* [11▪▪] examined chronic outpatient groups with schizophrenia ($n = 161$) and bipolar disorder I ($n = 130$), whereas the other three studies included mixed inpatient and outpatient samples of patients with schizophrenia spectrum disorders (SSD) and bipolar disorder I and II (Jabben *et al.* [13▪], $n = 345$ patients with SSD and $n = 76$ patients with bipolar disorder; Simonsen *et al.* [16▪▪], $n = 114$ patients with SSD and $n = 120$ patients with bipolar disorder), or schizophrenia and bipolar disorder I (Vaskinn *et al.* [19▪▪], $n = 154$ patients with schizophrenia and $n = 106$ patients with bipolar disorder I). With the exception of the study by Vaskinn *et al.* [19▪▪], a rather consistent finding is that, although psychosocial deficits are generally greater in patients with schizophrenia, neurocognition is associated with measures of functional outcome both in bipolar disorder and in schizophrenia. However, there also appear to be some differences; for example, Jabben *et al.* [13▪], who looked into various neuropsychological measures rather than a composite cognitive score, reported that the association between cognitive performance and psychosocial functioning was more generalized in patients with schizophrenia spectrum disorders, whereas in bipolar disorder it was restricted to performance on a selective attention task. Moreover, Bowie *et al.* [11▪▪] investigated not only direct relationships between neurocognition and functional outcomes, but also indirect relationships mediated through adaptive and social competence, that is, through the instrumental and communicative skills required for everyday functioning. These authors found that the mediation role of competence was more pronounced in bipolar disorder than in schizophrenia, with most of the relationship between cognition and real-world outcomes mediated by competence. Thus, it appears that the link between neurocognitive deficits and functional disability is stronger and more direct in schizophrenia, but still quite relevant in bipolar disorder [11▪▪].

RELATIVE CONTRIBUTIONS OF NEUROPSYCHOLOGICAL DEFICITS AND SYMPTOMS TO FUNCTIONAL OUTCOME IN BIPOLAR DISORDER

As seen above, neuropsychological deficits appear to influence the social and functional outcome in

patients with bipolar disorder. However, it has been suggested that cognitive deficits in bipolar disorder are largely dependent both on the severity and clinical course of the illness [28,29] and on the presence of residual minor affective symptoms, even during periods of clinical remission [30,31]. The issue is far from resolved, as other studies [28,32] have shown cognitive impairment to be independent of clinical symptoms during euthymic phases.

In this context, studies assessing the relative contributions of clinical symptoms and neuropsychological deficits to the functional outcome in patients with bipolar disorder have increasingly emerged in the past few years. Findings are rather consistent in studies investigating noneuthymic patient samples, with symptoms contributing to a greater extent to psychosocial dysfunction than neuropsychological deficits [16▪▪,17▪,18▪]. Moreover, in another study [11▪▪], the effects of neurocognition on functional outcome were both direct and mediated by adaptive and social competence measures, whereas clinical symptoms were mostly directly related to functioning. As the authors of this study discuss, it might be that the effects of symptoms on everyday behavior might occur at a post-competence level, not affecting the ability to perform skilled acts, but rather influencing the likelihood of performing them [11▪▪]. It should be stressed here that, in the vast majority of the studies mentioned above, the symptoms having a significant impact on function were depressive rather than manic symptoms. Regarding psychotic symptoms, the only study that has investigated their effect [16▪▪] reported no association with psychosocial outcome measures in patients with bipolar disorder.

However, the association between neurocognition, symptoms and functional outcome appears to be more complicated than the above findings suggest. A study conducted in euthymic patients with bipolar disorder [10▪▪] concluded that both neurocognition and symptoms contribute significantly to functional outcome, although the effect of the latter still appeared to be greater. In yet another study [20▪▪] investigating euthymic patients, cognitive ability was a more important predictor of global functioning than symptoms, although a primarily depressive course of the disorder also contributed to outcome. Moreover, Jabben *et al.* [13▪] found, in a mixed sample of inpatients and outpatients with bipolar disorder, that neurocognition had a significant effect on functionality even after accounting for the effects of clinical symptoms. Two further studies investigating patients with a long history of illness (at least 15 years) [12▪] and recently diagnosed patients after remission of a first manic episode [21▪▪], respectively, also found significant effects for both symptoms and cognitive deficits.

Although direct comparisons among studies are problematic due to significant methodological differences, a tentative conclusion is that symptoms are quite significant for functional outcome in bipolar disorder, but that neurocognitive deficits also have a role, which is more evident in asymptomatic or chronic patient samples.

OTHER AREAS OF POTENTIAL INTEREST

Parallel to an increasing number of studies dealing with the general topic of the association between neuropsychological performance and functional outcome in bipolar disorder, quite a few studies dealing with more focused aspects of this association have emerged in the past 2 years.

Bipolar disorder II

Bipolar disorder II was long considered to represent a milder form of bipolar disorder. However, recent research has shown that several dimensions of clinical outcome are more unfavorable in bipolar disorder II compared with bipolar disorder I [33]. Moreover, cognitive impairments in bipolar disorder II appear to be, for the most part, similar to those encountered in bipolar disorder I (for a recent meta-analysis, see [34]). Two studies have assessed the contribution of neuropsychological deficits to functional outcome in euthymic patients with bipolar disorder II compared with controls alone [35▪], or to euthymic bipolar disorder I patients as well [14▪▪]. Cognitive deficits were a significant predictor of psychosocial outcome in patients with bipolar disorder II in both studies. More importantly, the correlations between cognitive impairments and functional recovery were similar in patients with bipolar disorder I and bipolar disorder II in the second study [14▪▪], suggesting that the impact of neuropsychological deficits on functional recovery is independent of the subtype of bipolar disorder.

Social cognition

Social cognition, that is, the ability to perceive, interpret and respond to stimuli pertinent for social interaction, has received increasing attention in recent years. In patients with schizophrenia, various aspects of social cognition have shown a robust association with the functional outcome of the illness (e.g. [36]), and according to a recent meta-analysis are a better predictor of community functioning than nonsocial neuropsychological deficits in patients with schizophrenia [37]. In the past few

years, it has been repeatedly shown that bipolar disorder is also characterized by deficits in various aspects of social cognition, such as Theory of Mind and facial emotion recognition (for a recent meta-analysis, see [38▪]). Only one study has investigated the role of social cognition in the functioning of 39 euthymic patients with bipolar disorder I and II [39▪▪]. These authors reported that social cognition, more specifically Theory of Mind and emotion recognition, was a significant predictor of global functioning in patients in that study, along with subdepressive symptoms and nonsocial cognitive deficits (sustained attention).

Pediatric bipolar disorder

The neurocognitive profile of pediatric bipolar disorder appears to be similar to that of the adult illness, suggesting that many of the cognitive deficits found in bipolar disorder are present early in the course of the illness (e.g. [40]). On the basis of this observation, a recent study [41▪▪] investigated the contribution of neuropsychological deficits to psychosocial functioning in a sample of 138 patients with bipolar disorder aged 10–18 years. Results showed that the presence of cognitive deficits in youths with bipolar disorder significantly increased the risk for placement in a special class and lower academic achievement. However, in contrast to findings of studies in adult patients, neuropsychological impairment did not otherwise result in more psychosocial impairment. According to the authors, this result may have been due to the young age of patients: cognitive capacity might not be very relevant for psychosocial outcomes until a person enters adulthood, when demands in nonacademic domains (e.g. social and vocational) are increased. Further research in this area is of utmost importance in the design of interventions aimed at preventing psychosocial impairment in patients with early-onset bipolar disorder.

CONCLUSION

An overview of recent findings suggests that, although to a lesser extent than in schizophrenia, neurocognitive deficits are relevant for functional impairment in bipolar disorder as well. Attention and verbal memory appear to be the most plausible neuropsychological functions involved. However, affective (mainly depressive) symptoms appear to be a more important predictor of functional outcome in symptomatic patients, limiting the role of cognitive deficits to euthymic or chronic patients and stressing the importance of adequate symptom control. Future studies in larger patient populations with use of longitudinal designs, multiple functional outcome measures and consensually defined neuropsychological domains are warranted in order to confirm these conclusions.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 127–128).

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