Current Treatment Options for Cognitive Impairment in Bipolar Disorder: A Review

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Opinion Statement

Cognitive impairment is a key feature of bipolar disorder (BD) which often persists into euthymia. This impairment appears to be independent, to an extent, of mood symptoms and is associated with deficits in overall functioning. Priority should thus be given to research investigating adjunctive treatments aimed at improving cognitive functioning in BD. This paper systematically reviews studies specifically examining changes in cognitive functioning in relation to pharmacological and/or psychosocial interventions in adults with BD. Eighteen studies were included in the review; eleven examining pharmacological interventions and seven examining psychosocial interventions. Findings from the reviewed studies were mixed, but generally did not produce evidence of widespread cognitive improvement at treatment-end in line with widespread cognitive impairment considered to be a key feature of BD. It is, however, difficult to draw conclusions from the research to date due to the general scarcity of studies in the area, small sample sizes, minimal replication of studies examining the same intervention and variability in study designs. Future research in the area would benefit greatly from investigating the current reviewed interventions in large-scale RCTs. An understanding of what particular subgroups of BD patients gain most benefit from cognitive interventions would be of clinical use.

Introduction

Bipolar disorder (BD) is a complex mental illness that is considered within contemporary diagnostic systems as a primary mood disorder [1, 2]. Although it is defined by extreme fluctuations in emotion, cognitive impairment is becoming widely recognized as one of the core features of the illness [3]. Research over the past decade indicates substantial and persistent deficits across a broad range of cognitive domains including verbal learning, working memory and executive functioning [4-9]. Given that such deficits have been found at illness onset, in both BD I and BD II, as well as in relatives of those with the disorder, there is speculation that poor cognitive performance may represent a genetic susceptibility marker for the illness [10-13]. Generally, cognitive deficits in BD fall within half to one standard deviation below the control mean [9, 11] and may impact the capacity for social cognition [14-16]. Current mood symptomatology does appear to have some contribution to these impairments, but a substantial body of work assessing cognition in euthymic BD individuals also suggests that they persist even beyond symptom remission [17].

From a clinical standpoint, it is becoming increasingly clear that cognitive deficits in BD have substantial implications for functional outcomes [18, 19]. Persistent impairment in occupational and social functioning is a characteristic of many individuals with BD, conferring substantial economic burden on the economy through lost tax revenue and earnings due to occupational incapacity and welfare payments [20]. Although residual clinical symptomatology does play a role in such outcomes, a number of cross-sectional studies have now indicated relationships between both objective and subjective psychosocial functioning and neurocognitive ability in BD, independent of mood symptoms [21-23].

Further, compelling evidence from longitudinal studies also highlights the role of specific neurocognitive domains in predicting global, social and work functioning in BD [23-28].

Detrimental functional outcomes are not necessarily analogous to periods of illness versus recovery in BD [29, 30], it is clear that prioritising the study and development of strategies to improve cognition directly should remain a target for reducing psychosocial morbidity associated with the disorder. Progress to this end has been slow and there remains a general absence of methodologically-rigorous studies focussed on understanding the impacts of pharmacological agents or psychosocial interventions for improving cognition in BD, as compared with MDD [31]. Nevertheless some small gains have been made in this domain of late. This review provides an overview of the available studies in the area. Given that current treatment guidelines recommend the use of pharmacological agents as a first-line treatment coupled with adjunctive psychosocial treatment, this review is structured in line with these recommendations [32].

Methods

Research Question

How effective are 1) pharmacological and/or 2) psychosocial interventions in improving cognitive functioning in BD?

Search Strategy

Up to 1 February 2016, a systematic review of electronic databases was carried out for relevant papers, using MEDLINE, PubMed and Web of Science, based on the Cochrane method for reviews [33]. The following search terms were used: ‘bipolar disorder’ or

'mania*' *and* 'neuropsychological function*' or 'cognitive function*' or 'executive function*' or 'memory' *and* one term from one of the two following sections (depending on the section of the review the study was to be grouped under):

1. 'medication' or 'pharmacological treatment' or 'pharmacological intervention'
2. 'psychological intervention/treatment' or 'psychosocial intervention/treatment' or 'cognitive remediation/rehabilitation' or 'cognitive training'

Inclusion Criteria

Inclusion criteria were as follows:

- Interventional or observational studies in which a primary focus of paper was to ascertain objective cognitive and/or functional improvement
- Adult participants (all participants > 18 years of age)
- Assessment of cognitive functioning conducted at least twice, at baseline and post-treatment
- Sample including individuals diagnosed with BD (I or II), either symptomatic or in remission
- Not case studies (i.e., with sample size of > 1)

Exclusion Criteria

Of the studies that fulfilled inclusion criteria, a further seven were excluded for the following reasons:

- re-analysis of a particular sub-sample within a study already included in the review (i.e., in a BD II sample [34] and in a 'neurocognitively impaired' sample [35])

- inclusion of mixed psychosis and BD patient sample, with results from BD sample not reported separately [36-38] (study authors from these studies were unable to be contacted)
- follow-up cognitive functioning data not reported after cognitive remediation intervention [39]

It was common for studies to include mixed unipolar and BD depressed samples [40-42]. Studies were included on a case-by-case basis, depending on whether results from BD patients had been reported separately and depending on the ratio of unipolar: bipolar patients in the sample. Excluding these studies without the above considerations would have further constrained our ability to draw inferences about any potential benefits of cognitive remediation or psychological intervention in a significant portion of patients with BD. Authors of one of the above studies were contacted with regard to providing cognitive outcome data from their BD sample only, however, a response was not received prior to the date of manuscript submission [40]. The decision was made for this paper to remain in the review given that a substantial minority of their patient sample was diagnosed with BD (34-37% depending on the cognitive outcome assessed).

Assessment of Risk of Bias

Each randomised controlled trial (RCT) included in the review was assessed for risk of bias using the Cochrane Collaboration's tool for assessing bias [33], which includes the following domains: sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective outcome reporting, other sources of bias. These studies were then assessed as low risk of bias, unclear risk of bias, or high risk of bias. Our review was not

limited to RCTs; non-RCTs were categorised as having a high risk of bias due to being unable to meet Cochrane criteria for assessing bias (see Table 1).

Results

Eighteen studies met inclusion criteria (see Table 2), with 11 studies using a pharmacological intervention and seven studies using a psychosocial intervention. One of the pharmacological studies was included despite the analysis using a sample overlapping with a previous study. The decision was made to include this study [43] because it reported the results of an analysis of a separate neuropsychological variable from that presented in the original paper [44]. Given the overlap, the original study is reported when describing the patient/intervention characteristics below, but the study is separated from the original paper in Table 2 for clarity. One psychosocial intervention study [45] was a follow-up paper (one-year follow-up) of primary outcomes in a sample described in full in the original outcome paper of Torrent et al. (2013) [46].

Those studies assessed as being of a 'low risk of bias' were given greater emphasis in the review. An overview of the characteristics of studies relating to study design and sample characteristics will be provided in the appropriate sections below.

Pharmacological Intervention Studies

The pharmacological intervention studies investigated a wide variety of pharmacological agents including hormones controlling erythropoiesis [Erythropoietin; 47] and glucose levels [Insulin; 48], a dopamine agonist [Pramipexole; 43, 44], an antioxidant supplement [N-acetylcysteine; 49], acetylcholinesterase inhibitors [Donepezil; 50, Galantamine; 51, 52], a

glucocorticoid receptor antagonist [Mifepristone; 53, 54] and a nutraceutical [Withania Somnifera; 55].

With the exception of one study that did not include a control condition [i.e., placebo or healthy control group; 50], one 16-week open-label study [52], and one double-blind cross-over study with seven days of active treatment [53], all included studies were double-blind placebo-controlled trials. These parallel-group trials had active treatment lasting either seven days [54], or eight [44, 47, 51, 55], twelve [54] or 16 weeks [51] in length. Of the RCTs, two were assessed as having a low risk, five as an unclear risk, and two as a high risk of bias.

Patient Characteristics

Most studies included patients in full or partial remission [43, 44, 47, 50-52, 55] although some specifically recruited depressed BD patients [53, 54]. The mean age of the study samples generally ranged between 39 and 49 years of age, with the exception of one elderly sample with a mean age of 73 years [50]. Seven of the included studies had a slight predominance of female participants.

Intervention Characteristics

Studies were adjunctive trials in which a pharmacological agent was prescribed in addition to each participant's usual medication regime. Most studies reported that patients were stabilized on medication for at least two, but up to as much as six weeks prior to entering each study; and remained stable on medication from baseline to trial endpoint. Five studies [44, 50-52, 55] followed titration schedules in their dosing, while the others used fixed-dosing schedules across the trial period. Administration routes for the pharmacological agents included: oral [44, 49-55], blood infusion [47] and intranasal [48].

Study Findings

Of the eight RCTs, six reported improvements in selective cognitive domains for the active treatment condition, and two reported an absence of treatment effects. Two other open-label trials reported positive effects for the active agent. The results of studies are summarized below.

Pramipexole: Owing to an hypothesised role for aberrant dopaminergic signalling in cognitive impairment in BD, Burdick et al. [44] assessed the cognitive enhancing effects of pramipexole; a D2/D3 receptor agonist with current FDA approval as a treatment for Parkinson's Disease. In the full sample of BD completers, no significant improvements were seen in performance across several neurocognitive domains including executive functioning, processing speed, attention, verbal learning and fluency. However, effect sizes calculations did indicate greater improvement in the active treatment group (n=21) on the majority of measures. A secondary analysis conducted on a subgroup of euthymic BD patients from this sample revealed a generalised treatment effect in the pramipexole group, with specific improvements evident on tasks tapping verbal working memory and executive function. Although notable effect size benefits were seen in this euthymic group when compared to the full sample of completers on these measures, a separately published analysis of euthymic individuals from this trial [43] indicated that pramipexole had deleterious effects on risk taking activity as evidenced by an increase in disadvantageous choices made on a gambling task. Collectively this appears to suggest that pramipexole augmentation may be effective in remediating specific cognitive functions in non-symptomatic individuals with BD, with the trade-off being an increase in impulse control and risk-taking behaviour.

Mifepristone: Two separate trials by the same group were conducted to assess the effects of glucocorticoid receptor antagonist mifepristone on cognitive functioning in depressed individuals with BD. The initial pilot study [53] utilized a cross-over design with seven days of active treatment/placebo and a two-week follow-up period, while the subsequent trial [54] implementated a parallel groups design with seven days of active treatment and a six-week follow-up period. Results of the former trial indicated improvements in the mifepristone condition for spatial working memory, spatial recognition and verbal fluency; domains of cognition that are putatativley sensitive to corticosteroid elevation given their dependence on hippocampal function. Although this occurred in the presence of an improvement in mood symptoms, the antidepressant effect of mifepristone appeared to be independent of cognitive changes given that such changes occurred at a timepoint in which symptom ratings did not differ between the active compared with the placebo condition or baseline. The follow-up study supported the efficacy of mifepristone in enhancing spatial working memory. However, in this study the effect was only evident at six weeks post treatment, not at two weeks, as had previously been seen. Further, the effect was only evident in women, who in turn demonstrated a greater percentage of search errors on the spatial working memory task. In the context of past evidence indicating that progesterone augmentation impacts on spatial working memory, the authors speculated that such findings may indicate a mechanism for mifepristone's cognitive enhancing effects via progesterone antagonism. Since no other neuropsychological measures showed changes under the active condition, nor were there improvements in depressive symptoms, these findings suggest a selective and mood independent effect for mifepristone in improving spatial working memory in depressed individuals with BD.

Donepezil: A naturalistic open-label case series assessment examined the efficacy of donepezil, an acetylcholinesterase inhibitor labelled for use in Alzheimers Disease [50]. In an elderly BD sample followed over 12 weeks, no significant improvements were seen in cognitive functioning with the 10mg dose. Yet given that there is some evidence that donepezil confers benefit in treating cognitive impairment in neurological disease [56], and overlapping psychiatric disorders such as schizophrenia [57], it remains possible that the absence of findings here is attributable to the very small sample size. Alternatively, inadequate dosing may have been an issue given that on the basis of positive phase III trials occuring in the time since this study was published, the maximum FDA-recommended dosage for moderate cognitive impairment in Alzheimers Disease has increased from 10mg to 23mg [58]

Galantamine: Two separate trials tested the efficacy of galantamine, an FDA-approved Alzheimers Disease treatment that inhibits cholinesterase, but does so with a slighly different mode of action than donepezil [51, 52]. Both trials titrated galantamine slow release tablets up to the maximum 24mg dose (recommended for Alzheimers), and both reported improvements in verbal learning performance on the CVLT by trial end. Iosifescu et al [52] also reported improvements over time on a test of sustained attention, although caution should be drawn in interpreting these results given that this was an open-label trial with no placebo group. Nonetheless in this trial, cognitive improvements occurred alongside both a reduction in hippocampal Choline containing compounds (Cho) and an increase in hippocampal *N*-acetyl aspartate (NAA) as measured by magnetic resonance spectroscopy. Since higher levels of the former are associated with membrane breakdown and lower levels of the latter are associated with neuronal loss, the direction of these neurochemical changes over the trial period is consistent with the hypothesized neuroprotective role of galantamine. However, it is possible that the cognitive improvements seen here are quite selective, since

Ghaemi et al.[51] also observed improvements in the placebo condition for processing speed and semantic fluency measures that were not seen in the active treatment group. Unfortunately, the absence of a control group in the experimental design did not allow for clarification about whether this was attributable to an unfavorable impact of galantamine on processing speed, or alternatively whether the lack of change represents limits to the detection of change as a result of an absence of deficits in processing speed in the active treatment group to begin with.

N- acetylcysteine (NAC): Dean et al. [49] recently examined the cognitive enhancing effects of NAC for BD, in light of growing evidence for a role of oxidative stress and inflammation in cognitive impairment. This six-month RCT yielded no significant within- or between-group differences in change from baseline performance on any of the assessed cognitive domains of working memory, processing speed and executive function/fluency. The authors argue that it is possible that an insufficient treatment duration limited the capacity to see cognitive change. However, owing to the small sample size (total n=46) it is also highly likely that the abence of an effect was related to power restrictions more so than the absence of a true effect.

Intranasal Insulin: Preliminary evidence suggesting that dysregulation of insulin may be involved in neurocognitive function provided an impetus for McIntyre et al [48] to examime the cognitive enhancing effects of intranasal insulin in BD. In this RCT, euthymic individuals with BD I and II self-administered either placebo or insulin intranasally, four times per day over an eight-week trial period. To assess change over time, a broad cognitive battery was completed at baseline and endpoint. An additional cognitive assessment was completed one hour after intranasal adminstration to assess the acute effects of the active treatment. Over time, within-group improvements were evident, yet a significant group by time interaction

was shown for one measure only (Trail Making Test Part B); performance on this executive measure improved across the trial for the insulin, but not the placebo group. McIntyre and colleagues speculated that the lack of intranasal-insulin-positive-effects for the other cognitive measures may be associated with a lack of genotype stratification in their study given past interventional research showing an absence of treatment effect on verbal memory improvement with intranasal insulin in those with, but not without, the apolipoprotein E4 allele [59]. Thus it remains possibile that individuals carrying specific genotypes may represent a specific subpopulation that is responsive to intranasal insulin treatment.

Erythropoietin: Miskowiak et al.[47] examined the cognitive enhancing effects of erythropoietin, a red blood cell stimulating hormone that increases the oxygenating capacity of the blood. In this RCT, no treatment group improvements were evident for the primary outcome verbal learning at six weeks post-treatment. However, change from baseline cognitive scores at one week post-treatment did indicate slight improvements on the measure of verbal recall following interference. Significant and sustained improvements in the erythropoietin group were also evident for measures of sustained attention, social cognition and executive function. Since these improvements were evident in the absence of an improvement in mood, the authors suggested that the potential mechanism by which erythropoietin enacts its cognitive enhancing effect is independent of symptom resolution, and perhaps related to neuroplasticity or neurgenesis.

Withania somnifera: In the only known study assessing the effect of a medicinal plant on cognitive functioning in BD, Chengappa et al. [55] reported pro-cognitive effects for herbal agent withania somnifera over an eight week trial period. Specifically, greater improvements were seen in the active treatment group compared with placebo for verbal working memory,

processing speed and social cognition tasks at endpoint, but not at 4 weeks. Importantly, the working memory improvements translated to a moderate effect (*d*=0.5), but there were no significant improvements seen for measures of executive function or psychomotor speed. Thus this preliminary RCT suggests that withania somnifera may confer selective cognitive benefits in euthymic individuals.

Psychosocial Intervention Studies

Psychosocial interventions involved a form of cognitive remediation (cognitive or functional exercises aimed at improving cognitive and everyday functioning) [40, 45, 46, 60], specific training in social cognition [61], a psychological intervention (CBT; [62]), or a combination of psychological treatment (CBT) with cognitive remediation [63]. Three studies were RCTs [45, 46, 60], two were controlled clinical trials [61, 62], one was an open-label trial [63] and one was a case-controlled trial [40]. Two of the RCTs were investigating the same cognitive remediation intervention (termed 'functional remediation'), but reported data at two different follow-ups (post-treatment [46] and one year following treatment [45]). One RCT used treatment as usual (TAU) as the control condition [60], while the other two RCTs had two control conditions; a psychoeducation condition and a TAU [45, 46]. All of the RCTs were rated as having a low risk of bias (see Online Supplementary Material for details of this assessment). However, as part of this assessment, the Performance Bias domain (i.e., that study participants are blind to the intervention they are receiving) not taken into account for the overall risk of bias for each study, as this domain is extremely difficult to control for in psychological intervention studies.

Patient Characteristics

All seven studies included patients who were in remission or in partial remission from BD symptomatology. In all studies, patients were prescribed pharmacological treatment for BD, as deemed appropriate by their treating clinicians. The mean age of the study samples ranged from 34 years to 48 years and all samples were predominantly female.

Intervention Characteristics

The type of psychosocial intervention provided varied between studies. Of the cognitive remediation studies (*n*=5), two studies [45, 46] used a "functional remediation" intervention involving cognitive training (attention, executive functioning, and memory tasks) and performance of ecologically-relevant tasks at the clinic and at home. One study used a multimodal approach to cognitive remediation by including three components in each session: psychoeducation, training of strategies for cognitive dysfunction, and computer-assisted cognitive training [60]. A cognitive behavioural therapy (CBT) approach was used as a framework for incorporating cognitive training into sessions, such as organisational and memory skills and time management [63] in one study, and the remaining study used computerised tasks only aimed at improving various cognitive domains [40]. Of the remaining two studies in this section, one study examined the effect of an intervention aimed specifically at improving social cognition through use of emotional training, role-playing social situations, and integrating learning [61]. The final study examined the effect of CBT (not specifically targeting cognitive functions) on cognitive outcomes [62]. Five of the seven psychosocial intervention studies conducted their intervention in a group format [45, 46, 60-62]. The intensity of psychosocial interventions appeared to depend on the duration of the intervention, with briefer interventions involving a higher intensity (i.e., 3x weekly sessions over the course of 10 weeks [40]) and longer interventions being less intensive (i.e., weekly sessions or less for 4 to 6 months [45, 46, 61, 63]).

Study Findings

While all studies reported at least some significant improvement in functional or cognitive outcomes in relation to the psychosocial intervention, not all studies showed change in their primary outcome variable.

In their large-scale RCT in BD patients with moderate to severe functional impairment, Torrent et al. [46] reported significant improvement at treatment end (21 weeks) in their primary outcome variable, the Functional Assessment Short Test (FAST), in patients receiving group-based functional remediation compared with TAU, but not compared with a similar intensity group-based psychoeducation intervention. Two of the six domains from the FAST showed superiority in the functional remediation group compared with TAU: interpersonal and occupational functioning. Bonnin et al. [45]* published data from the same study at one-year follow-up and reported persisting improvement in FAST scores in the functional remediation group compared with psychoeducation and TAU groups. Within-group effect sizes for the functional remediation group from treatment end [46] to one-year follow-up [45] reduced from large to moderate (0.93 to 0.49). Only one domain from the FAST, autonomy, was found to be significantly different between groups at one year follow-up. Interestingly, while no significant changes in cognitive outcomes were found at treatment-end, verbal memory significantly improved from baseline to one-year follow-up in the functional remediation group compared with the other two groups. No other cognitive domains changed over time between treatment groups.

Demant et al. [60] conducted the only other known RCT of a psychosocial intervention directly targeting cognitive/general functioning in BD. No effect of their group-based

cognitive remediation intervention (*n*=18) was found on their primary outcome, verbal memory, compared with standard treatment (*n*=22) at treatment end (12 weeks) or at 26-weeks follow-up. In fact, of all neuropsychological and functional variables assessed in this study, only two specific variables improved significantly in the cognitive remediation compared with standard treatment group: subjective sharpness/mental acuity at 12 weeks, which was a single item on the CPFQ, and verbal fluency on the letter 'S' at 26 weeks.

In their open-label trial of a cognitive remediation intervention within a CBT framework (*n*=14), Deckersbach et al. [63] reported improved occupational (primary outcome) and psychosocial functioning in their BD sample. While changes in cognitive functioning from baseline to end-of-treatment were not specifically analysed in this study, improved executive functioning predicted improved occupational functioning. Docteur et al. [62] assessed explicit emotional memory in their controlled trial of CBT (without a specific cognitive remediation focus). The CBT group (*n*=42) significantly improved their recall of positive, neutral and total words, while reducing their recall of negative words, compared with the waitlist control group (*n*=15).

In an fMRI study of a purely computerised 10-week cognitive remediation intervention for patients with MDD or BD, Meusel et al. [40] examined working memory and verbal memory both in and out of the fMRI scanner pre- and post-treatment. Patients were significantly impaired in their backwards digit span performance compared with healthy controls at baseline, and showed significant improvement in this measure over the course of treatment, with this improvement correlating with the working memory task performed in the fMRI scanner (*n*-back task). Surprisingly, however, no association was found between improvement on backwards digit span performance and change in functional activation.

Finally, Lahera et al. [61]* examined Social Cognition and Interaction Training (SCIT), a treatment package originally designed for schizophrenia, as an adjunctive treatment to TAU (SCIT+TAU; *n*=21) versus TAU alone (*n*=16) in their sample of predominantly BD patients (*n*=4 patients were diagnosed with schizoaffective disorder). No difference between groups was observed in social functioning, as measured using the FAST, at treatment-end. The SCIT+TAU group performed significantly better over the course of treatment than the TAU group in emotion perception, theory of mind, and hostile attribution bias. Significant improvement in theory of mind was reduced to a trend when including only study completers (*n*=17 in SCIT+TAU group) in the re-analysis.

Discussion

Research focused on interventions aimed at improving cognitive functioning in BD is still in its infancy, with 70% of the reviewed studies published in the last five years (and all psychosocial intervention studies published in the last six years). Surprisingly little research has been conducted in this area given that widespread cognitive impairment is known to be a core feature of BD and significant associations exist between cognitive impairment and functional impairment [23]. Research is particularly scarce for studies assessing the efficacy of psychosocial interventions in BD.

In relation to the reviewed pharmacological treatment studies, conclusive inferences were challenging due to small sample sizes, minimal overlap between studies in the types of interventions assessed, and differing lengths of intervention and follow-up periods. Mifepristone and galantamine were each examined in two separate studies. Improvement in spatial working memory was evident in both studies of mifepristone, although effects were

limited to females in one of these studies [64]. Verbal learning and memory improvement was reported in an RCT [65] and open-label trial [66] of galantamine. No study reported convincing evidence of widespread improvement in cognitive functioning in treatment groups versus placebo-controlled groups. Generally, studies found improvement on specific measures of cognitive functioning within a broad battery of cognitive tests, or no significant effects of treatment on cognitive functioning. It is of note that some studies reporting improved cognitive functioning in relation to the active treatment also reported deleterious effects of active treatments on cognitive functioning [67] or significantly greater improvement in placebo versus treatment groups in particular domains of cognitive functioning [65]. Given that a broad range of cognitive functions are affected in BD, the findings from these studies do not offer promising evidence of any tested pharmacological agents conferring substantial cognitive improvement.

It is difficult to draw conclusions from the limited number of psychosocial intervention studies reviewed examining cognitive and/or functional outcomes in BD samples due to differences in study designs and primary outcomes measures, and great variability in study findings. Verbal working memory [40], verbal learning and memory [45] and social cognition/emotion processing [61, 62] appeared to show some evidence of change over time with cognitive remediation interventions, but some of the most scientifically-robust studies in this section did not report changes in these domains [46, 60].

Methodological Considerations

This section is not an exhaustive discussion of the limitations of the studies included in the current review, but a brief presentation of the salient issues that will be important to consider in planning future studies in this area.

Several studies followed an open-label format and lacked placebo/control groups, thereby limiting insight into the effectiveness of cognitive treatment over and above practice effects or normal improvement over time. The detection of ceiling effects or the establishment of clinically significant levels of cognitive impairment in BD samples was often impeded by lack of healthy control comparisons at baseline in many studies. Case – control comparisons at trial outset are important toward establishing a sufficient level of impairment that may be amenable to change. This is particularly relevant in light of anecdotal and empirical evidence of substantial heterogeneity in cognitive ability in BD [68, 69]. Indeed, a recent study reported that only ~40% of BD patients showed clinically important global cognitive impairment, with as much as 30% of patients demonstrating an absence of cognitive impairments at all [70]. Interestingly, a recent study investigated cognitive outcomes from a "neurocognitively-impaired" subsample of BD patients; the original RCT being reviewed in this paper [46]. While no significant cognitive improvement was found in the Functional Remediation versus TAU groups in the original RCT of 239 BD patients, re-analysis in only those patients with significant cognitive impairment to begin with (n=188) showed a significant improvement in a measure of verbal memory [35]. While this finding still does not provide strong evidence of widespread cognitive improvement in cognitively "impaired" BD samples, it does suggest that BD individuals with this particular cognitive profile may experience more cognitive gains from treatments directly targeting cognitive or everyday functioning.

Given the variability of clinical presentation and course for BD and the potential for subtle domain-specific differences in cognitive performance between the primary subtypes [10], power was an issue for most studies. A recent consensus statement on cognitive enhancement

trials for the disorder highlighted the importance of recruiting either large representative samples or smaller samples with narrowly defined phenotypes, as a means of meeting the challenges associated with establishing best-practice cognitive treatements for BD [70]. It is likely that the ability to detect the cognitive enhancing effects of given treatments in the studies reported here were affected by the general inclusion of small and fairly hetergoenous samples.

Further, not only did the reviewed studies include heterogeneous samples in terms of the clinical presentation of BD itself, but many included mixed MDD and BD samples. While this was in some ways useful in determining the cross-diagnostic effectiveness of cognitive interventions in larger samples, such over-inclusiveness also hampers the ability to draw meaningful conclusions in light of evidence that MDD and BD differ in terms of the qualitative and quantitive nature of their cognitive deficits [71-73].

The issue of multiple statistical comparisons is pertinent to the current review given that the most common finding from both pharmacological and psychosocial intervention studies was a significant improvement in a specific cognitive variable or measure, rather than widespread improvement across multiple cognitive measures or domains. Some studies corrected for multiple comparisons in their statistical analyses, however, some did not. It is, thus, likely that single significant findings in some studies may have been chance type 1 errors. An alternative approach when considering multiple comparisons is to make the decision *a priori* to examine patterns of results based on domains of cognitive functioning, and if isolated results occur, to interpret them cautiously.

Finally, the pharmacological studies were focussed on the effects of adjunctive treatments prescribed alongside each patient's usual treatment regime. Since the actions of these first-line treatments in interaction with novel pharmacological agents are likely to be complex, the impacts of variation in the use of concomitant medications on the study outcomes reported here are not clear. Therefore, future research assessing the effectiveness of novel cognitive treatments may aim to limit the recruitment of BD individuals using particular medication types, doses or polypharmacy, so as to gain a better understanding of the mechanisms by which any given treatment may be enacting an effect.

Social Cognition/Emotion Processing as a Treatment Target

As well as widespread impairment across traditional cognitive domains in BD, deficits in aspects of social cognition/emotion processing are well-cited in mood disorder research [74-79]. While research examining interventions directly targeting social cognition in BD is very limited, research focused on this domain in schizophrenia has produced encouraging findings. For example, a recent meta-analysis reported moderate to large effect sizes across studies examining interventions aimed at improving social cognition in schizophrenia, using measures of facial expression recognition (n=11; d=0.84) and theory of mind (n=10; d=0.70) as outcomes [80].

In the current review, five studies investigated changes in social cognition/emotion processing (facial emotion recognition: [55, 60, 61, 81], theory of mind: [61], emotional memory: [62]). Four of these studies reported significant changes in emotion processing in relation to treatment, with findings from three studies indicating that treatment resulted in a more positive, or less negative, response style to facial expressions (not necessarily more accurate [55, 81]) and improved recall of positively-valenced, but not negatively-valenced,

words [62]. To our knowledge, the only published study reporting cognitive and functional findings from an intervention directly targeting social cognition in BD was that of Lahera et al. [61], included in this review. They reported increased accuracy in recognising facial expressions of emotion and improved theory of mind. However, the well-cited negative attributional bias reported in mood disorder research [74] was not able to be examined in this study with their battery of social cognition tests. Further extending cognitive remediation interventions to encompass training in social cognition would be a useful area of future research in BD.

Conclusions

Interventions aimed at improving cognitive and functional outcomes in BD have not produced evidence of widespread improvement in line with the widespread cognitive impairment considered to be a key feature of the disorder. However, it is difficult to draw conclusions from research to date due to the general scarcity of studies in the area, small sample sizes, minimal replication of studies examining the same intervention and variability in study designs. What has been made clear from the current review is that for knowledge about the effectiveness of cognitive treatments in BD to expand, substantially more large-scale studies involving well-considered control groups and logical statistical methods allowing for multiple cognitive comparisons in purely BD samples is required. It moving forward, it will be important to gain a better understanding in what particular subgroups of BD patients gain the most benefit from interventions aimed at improving cognitive functioning. Additionally, psychological therapies that involve components of cognitive training (e.g., metacognitive therapy) are being investigated for clinical effectiveness for various mental health conditions at present, and including cognitive outcomes in these studies would be a valuable addition.

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Conflicts of interest

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Table 1. Assessment of Risk of Bias for RCTs Included in Review (in Order of Publication Date)

	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall Rating
Pharmacological Intervention RCTs							
Young et al. (2004) [1]	**Unclear** for Random Sequence Generation* **Unclear** for Allocation Concealment	**Unclear***	**Unclear***	**Low**	**Unclear** (study protocol not available)	**Low**	**Unclear**
Ghaemi et al. (2009) [2]	**Low** for Random Sequence Generation **Low** for Allocation Concealment	**Low**	**Low**	**High** (imbalance in numbers dropping out between groups and no reason specified)	**Unclear** (no a-priori primary outcomes specified due to lacking research in area)	**Low**	**High**
Burdick et al. (2012) [3]	**Unclear** for Random Sequence Generation* **Unclear** for Allocation Concealment	**Unclear***	**Unclear***	**Low**	**Low**	**Low**	**Unclear**
Dean et al. (2012) [4]	**Low** for Random Sequence Generation **Low** for Allocation Concealment	**Low**	**Low**	**Low**	**NA** (follow-on paper from RCT on efficacy of medication - but cognition not stated as primary outcome in Australian Clinical Trial registration for full RCT)	**Low**	**Low**

	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall Rating
Pharmacological Intervention RCTs continued…							
McIntyre et al. (2012) [5]	**Low** for Random Sequence Generation **Unclear** for Allocation Concealment	**Unclear***	**Unclear***	**Unclear** (reduced sample size on some cognitive tests with reason for reduction not provided)	**Low**	**Low**	**Unclear**
Watson et al. (2012) [6]	**Low** for Random Sequence Generation **Low** for Allocation Concealment	**Low**	**Low**	**Unclear** (appears to be missing data in cognitive tests according to reporting of statistics in paper but reason for missing data not explained)	**High** (spatial working memory reported as primary outcome measure in paper, but general neurocognitive function reported as primary outcome in clinical trial registration protocol)	**Low**	**High**
Chengappa et al. (2013) [7]	**Low** for Random Sequence Generation **Unclear** for Allocation Concealment	**Low**	**Unclear –** no mention of how/if neuropsych assessor was blind	**Low**	**Low**	**Low**	**Unclear**
Burdick et al. (2014) [8]	**Unclear** for Random Sequence Generation* **Unclear** for Allocation Concealment	**Unclear***	**Unclear***	**Low**	**NA** (paper describes findings of an additional cognitive measure included in Burdick et al. (2012) RCT [3] after study commenced)	**Low**	**Unclear**

	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall Rating
Pharmacological Intervention RCTs continued…							
Miskowiak et al. (2014) [9]	**Low** for Random Sequence Generation **Low** for Allocation Concealment	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Psychosocial Intervention RCTs							
Torrent et al. (2013) [10]	**Low** for Random Sequence Generation **Unclear** for Allocation Concealment	**Unclear/NA**	**Low**	**Low**	**Low**	**Low**	**Low**
Demant et al. (2015) [11]	**Low** for Random Sequence Generation **Low** for Allocation Concealment	**Unclear/NA**	**Low**	**Low**	**Low**	**Low**	**Low**
Bonnin et al. (2016) [12]	**Low** for Random Sequence Generation **Unclear** for Allocation Concealment	**Unclear/NA**	**Low**	**Low**	**Low**	**Low**	**Low**

*study endorses having used the criterion above in the study design to reduce bias, but does not describe in enough detail to assess for risk of bias in the paper (e.g., study is described as “double blind” in the paper but no further information in the paper is provided about how blinding was carried out or ensured OR study is described as “randomised” in the paper but no further information in the paper is provided about how randomisation was carried out or ensured).

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Table 2. Reviewed Studies

Author / Date	**Sample Diagnosis**	**Symptom Status**	**Intervention/Design**	**Sample Size of Completers**	**Duration**	**Cognitive Assessment Battery (*primary outcome underlined, if applicable*)**	**Key Findings**	**Risk of Bias**
Pharmacological Interventions (ordered according to type of intervention)								
Burdick et al. (2012)	DSM-IV BD	Affectively stable (defined as score of < 6 CARS-M and ≤ 12 HAM-D 17)	Pramipexole 1 = pramipexole 2 = placebo (adjunctive double-blind, randomised, placebo-controlled parallel groups design)	1 n=21 2 n=24 *Euthymic subsample* 1 n=16 2 n=19	8 weeks	- WAIS-III subtests: Digit-Symbol Coding, Digit Span - Stroop Test - Trail Making Test A + B - d2 Test of Attention - Hopkins Verbal Learning Test - COWAT Primary outcome: change from baseline scores on all cognitive tests	Full Completers Sample: non-significant treatment group effect. Stroop Test reached uncorrected statistical significance (p=0.03), with a greater improvement in performance noted in pramipexole group. Larger (albeit non-significant) effect sizes noted in pramipexole group than in the placebo group on 8/11 measures. Euthymic Subgroup: significant overall effect of treatment group on neurocognitive functioning. Significantly greater improvement found in pramipexole group for Digit Span Backwards and Stroop Test. Effect size differences indicated enhanced benefit of pramipexole in euthymic subgroup compared with full completers sample.	Unclear
Burdick et al. (2014)	DSM-IV-TR BD	Euthymic BD (subset of full completers sample from Burdick et al. 2012)	Pramipexole 1 = pramipexole 2 = placebo (adjunctive double-blind, randomised, placebo-controlled parallel groups design)	1 n=16 2 n=18	8 weeks	Iowa Gambling Task	Pramipexole group showed a performance pattern analogous to a reverse learning curve, attended more to gains than to losses after treatment.	Unclear

Table 1. Reviewed Studies – continued…

Author / Date	**Sample Diagnosis**	**Symptom Status**	**Intervention/Design**	**Sample Size of Completers**	**Duration**	**Cognitive Assessment Battery (*primary outcome underlined, if applicable*)**	**Key Findings**	**Risk of Bias**
Watson et al. (2012)	DSM-IV BD I or II in depressed phase and HC (for baseline comparison)	Current depressed episode as defined by the SCID-I	Mifepristone 1 = Mifepristone 2 = Placebo 3 = HC (adjunctive, double-blind, randomised, placebo-controlled, parallel group design with a HC)	1 n=30 2 n=30 3 n=55	7 days, and follow-up over 6 weeks	- CANTAB Spatial Working Memory, Spatial Span, Pattern Recognition, Spatial Recognition - RAVLT - Phonological Fluency - Digit Symbol Substitution Test Primary outcome: changes in Spatial Working Memory	Women in the mifepristone group showed sustained improvement in spatial working memory 6 weeks after treatment. No significant effects for the other neuropsychological measures.	High
Young et al. (2004)	DSM-IV BD	At baseline, all patients had persistent depressive symptoms, with 17 fulfilling SCID criteria for current depressive episode	Mifepristone (adjunctive, double-blind, randomised, placebo-controlled, cross-over design)	n=19	7 days, and follow-up over 2 weeks, followed by cross-over	- CANTAB Spatial Working Memory, Spatial Span, Phonological Span forwards, Pattern Recognition, Spatial Recognition - RAVLT - Phonological Fluency - Digit Symbol Substitution Test - Continuous Performance Test – VIGIL Primary outcome: Spatial Working Memory and RAVLT	Spatial working memory function was significantly improved from baseline after mifepristone compared with placebo. Improvements were seen in verbal fluency and spatial recognition memory following mifepristone.	Unclear
Gildengers et al. (2008)	Elderly BD I or II (diagnostic criteria not specified)	Euthymia (defined as YMRS and MADRS scores of ≤ 10)	Donepezil (open label, naturalistic, pilot study)	n=9	12 weeks, and 3 months follow-up	*Cognitive* - Digit Span forwards + backwards - Trail Making Test A + B - Digit-Symbol Coding - Stroop Test *Functional* - Instrumental Activities of Daily Living Primary outcome not specified	Numerical changes on cognitive and functional test scores from time 1-2, but no significant improvements.	High (not RCT)

Table 1. Reviewed Studies – continued…

Author / Date	**Sample Diagnosis**	**Symptom Status**	**Intervention/Design**	**Sample Size of Completers**	**Duration**	**Cognitive Assessment Battery (*primary outcome underlined, if applicable*)**	**Key Findings**	**Risk of Bias**
Ghaemi et al. (2009)	BD I or II (diagnostic criteria not specified)	Euthymia (defined as MRS score of ≤ 15 and MADRS score of ≤ 10)	Galantamine (slow release) 1 = Galantamine 2 = placebo (adjunctive, double-blind, randomised, placebo-controlled, parallel groups design)	1 n=16 2 n=10	12 weeks	- D-KEFS subtests: Trail Making Test, Verbal Fluency - WCST - CVLT-II No primary outcome specified due to lack of evidence for an effect of galantamine on a specific cognitive measure	CVLT-II total learning improved in the galantamine group but not the placebo group. Placebo group but not the galantamine group showed improved performance on two D-KEFS Trail-Making conditions and in Category Fluency.	High
Iosifescu et al. (2009)	DSM-IV BD and HC	Remission (defined as HAM-D 17 or YMRS scores of ≤ 10)	Galantamine (slow release) 1 = BD (galantamine) 2 = HC (adjunctive, open label trial, compared with HC)	1 n=11 2 n=10	16 weeks	*Cognitive* - Conner's Continuous Performance Test - CVLT - WCST *Imaging* BD group (n=8) had repeat 1H-magnetic resonance spectroscopy (MRS; proton spectrum acquired from 2 separate voxels localised on left and right hippocampus) Primary outcome: change from baseline on Continuous Performance Test commission errors, CVLT Trial 1, Trial 1-5, WCST total errors and failure to maintain set	BD group experienced significant improvement on the Continuous Performance Test and the CVLT after treatment. In BD patients with MRS scans, Cho (Choline containing compounds) levels decreased over the trial in the left hippocampus; *N*-acetyl aspartate levels increased in the left but not in the right hippocampus during the trial.	High (not RCT)
Dean et al. (2012)	DSM-IV BD I or II	Bipolar disorder in the maintenance phase (on stable therapy for at least 1 month prior to recruitment)	N-acetylcysteine (NAC) 1 = NAC 2 = placebo (adjunctive, double-blind, randomised, placebo-controlled, parallel groups design)	1 n=21 2 n=25	24 weeks	- Digit Span forwards + backwards - Word Learning - Trail Making Test A + B - Verbal fluency Primary outcome: not specified as this is a study of a subset of patients from a larger trial of which cognition was one outcome	No significant differences between NAC or placebo groups at trial end for any of the cognitive measures. No within group changes between baseline and trial end in the NAC group.	Low

Table 1. Reviewed Studies – continued…

Author / Date	**Sample Diagnosis**	**Symptom Status**	**Intervention/Design**	**Sample Size of Completers**	**Duration**	**Cognitive Assessment Battery (*primary outcome underlined, if applicable*)**	**Key Findings**	**Risk of Bias**
McIntyre et al. (2012)	DSM-IV BD I or II	Euthymia (defined as score of ≤ 3 on HAM-D 17 and ≤ 7 on YMRS)	Intranasal Insulin 1 = insulin 2 = placebo (adjunctive, double-blind, randomised, placebo-controlled, parallel groups design)	1 n=21 2 n=22 (statistics of completing sample only not reported)	8 weeks	*Cognitive* - CVLT-II - Process Dissociation Task - Trail Making Test A + B - Digit Symbol Substitution Test - COWAT - Category Fluency - Visual Backward Masking Test - Shipley Institute of Living-Abstraction Test - Continuous Visual Memory Test *Subjective Cognitive Measures* - Cognitive Failures Questionnaire Primary outcome: change from baseline on CVLT-II and Process Dissociation Task	A single significant Treatment x Time interaction was found for Trail Making Test Part B, with insulin group improving significantly more than placebo group at endpoint.	Unclear
Miskowiak et al. (2014)	ICD-10 BD I or II	Partial remission (defined as HAM-D 17 and YMRS scores ≤ 14)	Erythropoietin 1 = Erythropoietin 2 = Placebo (adjunctive phase, two double-blind, randomised, placebo-controlled parallel groups design)	1 n=23 2 n=20	8 weeks, and follow-up at 6 weeks post-treatment	- RAVLT - Rapid Visual Processing - Trail Making Test A + B - Verbal Fluency (letters) - WAIS-III Letter Number Sequencing - RBANS: Digit Span, Coding - Facial Expression Recognition Primary outcome: change from baseline on RAVLT trials 1-5	In erythropoietin group, there was no effect on verbal memory but there was improvement in sustained attention, social cognition, and executive function. Highly significant, long-lasting improvements were seen on a composite score of complex cognitive processing speed (memory, executive function and attention) in the erythropoietin group	Low
Chengappa et al. (2013)	DSM-IV BD I, II or NOS	Euthymia (defined as YMRS and MADRS scores of < 10)	Withania Somnifera (WSE) 1 = WSE 2 = placebo (adjunctive, double-blind, randomised, placebo-controlled trial, parallel groups design)	1 n=24 2 n=29	8 weeks	- Set Shifting Test - Strategic Target Detection Test - Flanker Test - Auditory Digit Span - Word List Memory - Finger Tapping Test - Penn Emotional Acuity Test Primary outcome: change from baseline scores on all cognitive tests	Significantly greater improvement in Withania Somnifera group compared with placebo for Auditory Digit Span, neutral mean response time on the Flanker Test, and mean social cognition response rating on Penn Emotional Acuity.	Unclear

Table 1. Reviewed Studies – continued…

Psychosocial Interventions (ordered according to type of intervention)								
Author / Date	**Sample Diagnosis**	**Symptom Status**	**Intervention/Design**	**Sample Size of Completers**	**Duration and Intensity**	**Cognitive / Functional Assessment Battery (*primary outcome underlined, if applicable*)**	**Key Findings**	**Risk of Bias**
Torrent et al. (2013)	DSM-IV BD	In remission for 3 months (defined as score of ≤ 8 on HAM-D and ≤ 6 on YMRS for 3 months before study enrolment) but with severe functional impairment (FAST total score ≥ 18) On stable medication during intervention	<u>Cognitive Remediation</u> 1 Functional remediation (FR) – group format 2 Psychoeducation (PE) – group format 3 TAU (RCT)	1 n=55 2 n=64 3 n=66	1x 90 min weekly sessions for 21 weeks (for both FR and PE)	*Cognitive* - WAIS-III subtests: Vocabulary, Digit-Symbol Coding, Symbol Search, Arithmetic, Digit Span, Letter-Number Sequencing - Wisconsin Card Sorting Test - Stroop Test - Controlled Oral Word Association Test - Trail Making - Rey-Osterrieth Complex Figure - CVLT - Logical Memory Scale - Continuous Performance Test *Functional* - Functional Assessment Short Test (FAST) <u>Primary outcome: change in FAST score</u>	Improved global psychosocial functioning (FAST) at the end of treatment (21 weeks). All improved over treatment but FR > TAU, but did not differ from PE on the FAST. FR > TAU in Interpersonal domain and Occupational domains on the FAST. Within group ES – FR: *d*=0.93, PE: *d*=0.41, TAU: *d*=0.22. Between group effect sizes: FR *vs* TAU 0.3, PE *vs* TAU -.09. Improved neuropsychological performance for all groups over time but no significant differences between groups.	Low
Bonnin et al. (2016) *1-year follow-up of Torrent et al. (2013)*	*As above*	*As above*	*As above*	1 n=54 2 n=60 3 n=58	*As above*	*As above*	Improved global psychosocial functioning (FAST) in FR group compared with PE and TAU at 1 year follow-up. Within group ES – FR: *d*=0.49 (other groups not reported). Between group ES for FR *vs* TAU *d*=0.18. FR > PE and TAU in Autonomy domain of FAST. FR > PE and TAU in verbal memory. No between-group differences were found in any other neuropsychological domains over time.	Low

Table 1. Reviewed Studies – continued…

Author / Date	**Sample Diagnosis**	**Symptom Status**	**Intervention/Design**	**Sample Size of Completers**	**Duration and Intensity**	**Cognitive / Functional Assessment Battery (*primary outcome underlined, if applicable*)**	**Key Findings**	**Risk of Bias**
Demant et al. (2015)	ICD-10 BD	In full or partial remission (defined as HAM-D 17 and YMRS ≤ 14) Subjective cognitive difficulties according to the Cognitive and Physical Failures Questionnaire (CPFQ; > 4 on > 2 domains)	Cognitive Remediation 1 Cognitive Remediation (CR) – group format 2 Standard Treatment (ST) – medications with or without psychoeducation (RCT)	1 n=18 2 n=22	1x 2 hr weekly sessions for 12 weeks + booster session 4 weeks after end of treatment	*Cognitive* - Rey Auditory-Verbal Learning Test (RAVLT) - Trail Making Test - RBANS: Coding, Digit Span - CANTAB: Rapid Visual Information Processing, Delayed Matching to Sample, Spatial Working Memory, Simple Reaction Time - WAIS-III: Letter-Number Sequencing - Verbal Fluency - Facial Expression Recognition *Functional* - FAST, CPFQ, Cognitive Failures Questionnaire, WHO Quality of Life BREF, Cohen's Perceived Stress Scale, European Quality of Life, Work and Social Adjustment Scale Primary outcome: change in RAVLT	No improvement of CR over ST on any measure of the primary outcome (RAVLT) post-treatment. No neuropsychological or functional measures were significantly different between CR and ST groups at post-treatment. CR significantly improved subjective mental acuity (single item from CPFQ) post-treatment (p=0.013) and one measure of verbal fluency (letter 'S') at 26 weeks follow-up (p=0.005).	Low
Meusel et al. (2013)	DSM-IV MDD or BD HC	Euthymic or residual symptoms (no specific HAM-D or YMRS cut-off, but not acutely unwell)	Cognitive Remediation 1 Computer assisted cognitive remediation – individual format 2 Different healthy control groups for each of the two different tasks (Case control)	Task 1: *n*-back 1 n=23 CR 2 n=15 HC Task 2: memory 1 n=28 CR 2 n=18 HC	1x 1hr sessions per week for 10 weeks	*Cognitive* - Hopkin's Verbal Learning Test-Revised (HVLT-R) - Digit Span – backwards - Object *n*-Back Task (during fMRI) - Recollection Memory Task (during fMRI) Primary outcome: not specified	Deficits observed in working memory, recollection memory but not delayed memory at pre-treatment in CR group *vs* HC. Working memory (Digit Span, p=0.04) improved in CR group over time, with detectable changes on fMRI scanning in relation to *n*-back task performance. Improved Digit Span performance in CR group unable to be directly associated with fMRI changes in frontal and parietal regions.	High (not RCT)

Table 1. Reviewed Studies – continued…

Author / Date	**Sample Diagnosis**	**Symptom Status**	**Intervention/Design**	**Sample Size of Completers**	**Duration and Intensity**	**Cognitive / Functional Assessment Battery (*primary outcome underlined, if applicable*)**	**Key Findings**	**Risk of Bias**
Deckersbach et al. (2010)	DSM-IV BD I and II	Residual or no symptoms (defined as score of ≤ 12 on HAM-D 17 and ≤ 8 on YMRS, no mood episodes in 8 weeks preceding recruitment) On stable medication	Cognitive Remediation/CBT 3 modules – individual format 1st module: mood monitoring and treatment of residual symptoms (CBT, social rhythms); 2nd module: organisation, planning, time management; 3rd module: attention and memory. (Open trial)	n=14 (n=17 in ITT analysis)	14 x 50 min sessions over 4 months	*Cognitive* - RBANS - D-KEFS subtests: Trail Making, Card Sorting *Functional* - Health Performance Questionnaire (assesses occupational functioning) - Longitudinal Interval Follow-Up Evaluation – Range of Impaired Functioning Tool (assesses psychosocial functioning) - Frontal Systems Behavior Rating Scale (FrSBE) (assesses executive functioning in daily life) Primary outcome: Health Performance Questionnaire	Significant improvement in occupational (p=0.001) and psychosocial functioning (p=0.03), and executive functioning (FrBSE; p=0.003) at post-treatment, which remained at follow-up (3 months post-treatment). Improved executive functioning (FrBSE) predicted improved occupational functioning. No correlations between any neuropsychological measure and pre-treatment occupational functioning. Less improvement in those with worse pre-treatment neuropsychological functioning.	High (not RCT)
Lahera et al. (2013)	DSM-IV BD I and II, and schizo-affective disorder	Euthymia (defined by absence of affective relapse for ≥ 3 months)	Social Cognition and Interaction Training (SCIT) 1 SCIT+TAU – group format (3 phases: emotional training, role-play, integration) 2 TAU (Controlled clinical trial)	1 n=17 2 n=16 (re-analysis conducted with schizo-affective patients excluded)	1 hr sessions for 18-24 weeks	*Social Cognition* - Face Emotion Identification Task - Face Emotion Discrimination Task - Emotion Recognition-40 Task - Hinting Task (theory of mind) - Ambiguous Intentions Hostility Questionnaire *Functional* - FAST Primary outcome: not specified	No difference between SCIT+TAU and TAU groups in social functioning (FAST), but SCIT+TAU group showed significant improvement in measures of emotion perception and hostile attribution bias and a trend for improvement in theory of mind. Between-group effect sizes for significant differences and trends were large.	High (not RCT)
Docteur et al. (2013)	DSM-IV BD	In remission (specific definition not reported) On stable medication	CBT 1 CBT – group format 2 Waitlist Control (Controlled clinical trial)	1 n=42 2 n=15	< 5 months	- Explicit Memory Task (involving recall of words of positive, negative or neutral valence) Primary outcome: not specified, only one cognitive measure	Significant Time x Group x Valence interaction. Explained by improvement in positive (p<0.001), neutral (p=0.03) and total recall (p=0.004) of words, and decrease (p=0.02) in negative words after CBT.	High (not RCT)

Abbreviations: BD = Bipolar Disorder, **CARS-M** = Clinician Administered Rating Scale for Mania, **CBT** = Cognitive Behavioural Therapy, **COWAT** = Controlled Oral Word Association Test, **CPFQ** = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, **CVLT** = California Verbal Learning Test, **D-KEFS** = Delis-Kaplan Executive Function System, **ES** = effect size, **FAST** = Functioning Assessment Short Test, **FrSBE** = Frontal Systems Behavior Rating Scale, **HC** = healthy control, **HRSD** = Hamilton Rating Scale for Depression, **ITT** = Intention to Treat, **MADRS** = Montgomery-Asberg Depression Rating Scale, **MDD** = Major Depressive Disorder, **MRS** = Mania Rating Scale, **RBANS** = Repeatable Battery of the Assessment of Neuropsychological Status, **WAIS-III** = Wechsler Adult Intelligence Scale – 3rd edition, **WCST** = Wisconsin Card Sorting Test, **YMRS** = Young Mania Rating Scale