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Efficacy of cognitive remediation in bipolar disorder: systematic review and meta-analysis of randomized controlled trials

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Review Article

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Abstract

A significant percentage of people with bipolar disorder (BD) exhibit suboptimal functional adjustment, even when appropriately treated and after symptomatic recovery is achieved. Given that cognitive impairment is one of the strongest correlates of socio-occupational outcomes and quality of life in BD, cognitive remediation (CR) is currently acknowledged as a promising treatment that could help bridge the gap between symptomatic and full functional recovery. The aim of this review was to explore the efficacy of CR approaches in improving cognitive and functional outcomes in BD patients. PubMed, PsycINFO, and CENTRAL were searched from inception to November 2022. Randomized controlled trials exploring the effects of CR on cognition and/or functional adjustment in adult BD patients were eligible. Ten studies based on seven independent trials ($n = 586$) were included. Change-score effect sizes (Hedges' g) were obtained for efficacy outcome measures and combined by means of meta-analytic procedures. Small but significant overall effects were observed for working memory ($g = 0.32$, 95% CI 0.11–0.52), planning ($g = 0.30$, 95% CI 0.03–0.56), and verbal learning ($g = 0.40$, 95% CI 0.15–0.66). However, CR was not found to exert any significant effects on functional outcomes at treatment completion or at follow-up assessment. Although CR may modestly enhance the cognitive performance of BD patients, this effect does not translate into an improvement at the functional level. The current data do not support the inclusion of CR as a treatment recommendation in clinical practice guidelines for the management of BD.

Introduction

A significant percentage of people with bipolar disorder (BD) exhibit conspicuous functional impairments even when appropriately treated and after symptomatic recovery is achieved (Gitlin & Miklowitz, 2017; Mignogna & Goes, 2022; Tsapekos, Strawbridge, Cella, Wykes, & Young, 2021). Therefore, recovery of functional capacity is currently acknowledged as a key treatment goal in the clinical management of BD patients.

Measurable neuropsychological impairments are present in a substantial proportion of affected individuals across attention, processing speed, episodic memory, and different domains of executive functioning (Jones et al., 2022; Montejo et al., 2022; Robinson et al., 2006). These impairments are related to mood symptoms but persist with varying magnitude and extension during euthymia in about two thirds of BD patients (Ehrlich et al., 2022; Keramatian, Torres, & Yatham, 2022) and represent major predictors of poor quality of life and suboptimal outcomes in different aspects of real-world functioning (Ehrminger et al., 2021; Gitlin & Miklowitz, 2017; Tsapekos et al., 2021). Consequently, the importance of identifying individuals with impaired neuropsychological performance has become widely recognized, and evidence-based treatments targeting cognition have received increasing interest over the last few years (Tamura et al., 2021; Tsapekos et al., 2020). Within this context, pharmacological, neurostimulation, and psychosocial approaches have been proposed with the aim of restoring or improving the functional capacity of BD patients (Miskowiak et al., 2022; Tamura et al., 2021). Among psychological interventions, cognitive remediation (CR) stands out as an emerging treatment with potential pro-cognitive effects (Miskowiak et al., 2018; Tsapekos et al., 2020). CR approaches are frequently included in the clinical management of individuals with psychotic disorders based on the consistent evidence of modest though significant effects on both cognitive and functional outcomes (Kambeitz-Ilankovic

et al., 2019; Lejeune, Northrop, & Kurtz, 2021; Vita et al., 2021). Broadly speaking, CR includes different behavioral interventions targeting cognition by means of cognitive training and compensation techniques with the aim of improving functional adjustment (Bellani et al., 2019; Miskowiak et al., 2018). Functional remediation is a variant of standard CR designed specifically for BD patients that tackles cognitive impairments within an ecologic framework while providing psychoeducation about neuropsychological impairment and its impact on daily functioning (Bonnin et al., 2016a, 2016b; Torrent et al., 2013).

Although not yet included as an evidence-based recommendation in the main treatment guidelines for BD (Malhi et al., 2020; Yatham et al., 2018), CR is increasingly acknowledged as a promising psychosocial intervention (Miskowiak et al., 2018; Montejo et al., 2022; Tsapekos et al., 2020). However, only a few randomized controlled trials (RCTs) exploring the efficacy of CR in BD are available at present; most of them are underpowered and yield inconsistent results.

This study aimed to review the evidence from RCTs exploring the efficacy of CR interventions in improving cognitive and functional outcomes in BD patients and to combine the findings of individual trials to obtain overall effect sizes for different efficacy outcome measures at different timepoints.

Method

Registration and study protocol

This study was conducted in accordance with the PRISMA 2020 Statement guidelines (Page et al., 2021) (online Supplementary Table S1). The review protocol was registered (PROSPERO, CRD42022306504) and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022306504.

Search strategy

PubMed, PsycINFO, and the Cochrane Collaboration Controlled Trials Register were searched from inception until 1 November 2022 to retrieve publications. Any language was considered as long as an abstract in English was available. At the first step of the search, combinations of keywords were used as follows: (bipolar OR bd OR manic depress*) AND (cognit* OR neurocognit* OR neuropsycholog*) AND (remediation OR rehabilitation OR training OR enhancement OR therapy) AND (efficacy OR randomized trial OR rct).

Titles and abstracts retrieved using this strategy were screened to identify relevant studies. Full texts of the articles identified in this initial screening were thoroughly assessed to confirm or reject their inclusion based on prespecified criteria. As a second step, the reference lists of the articles identified for inclusion and other relevant studies on the topic (e.g. systematic reviews) were checked for additional eligible reports. All the steps of the literature search were conducted independently by two reviewers (PD, BLC). Disagreements were resolved by consensus-based discussion.

Study selection criteria

Studies were considered for inclusion in the current review if they met the following criteria:

(1) were RCTs;
(2) included adult patients (age > 18 years) diagnosed with BD according to standardized criteria;
(3) compared changes in cognitive and/or functional outcomes between a group of patients receiving CR and a control group;
(4) used standardized instruments to assess outcome measures; and
(5) provided data to estimate between-group effect sizes for neuropsychological/functional change.

The RCTs reviewed were included in the quantitative synthesis if they explored at least one cognitive or functional variable assessed in a minimum of three independent trials. If there were studies with overlapping content based on the same patient sample, only the highest-quality study was included in the meta-analysis. Two studies based on the same sample were included in the quantitative synthesis if they provided different information that could be meta-analyzed separately (i.e. data for different variables or assessment time points) and only one (the study with the largest sample size) was considered in the total patient count. Studies based on samples of patients with different diagnoses were included as long as separate data for BD patients were available from the original authors.

Data extraction and risk of bias assessment

Two reviewers (PD, BLC) independently extracted the following data from each RCT: first author and year of publication, sample size, age, gender, study design, type of CR intervention, characteristics of the control group, assessment time points, outcome measures, and discontinuation rates. Results on neuropsychological and functional measures at baseline, treatment completion, and follow-up assessment (when available) were extracted for both treatment and control groups. A consensus meeting was held to resolve any disparities between the two reviewers. Version 2 of the Cochrane risk-of-bias tool for randomized trials (Sterne et al., 2019) was used to appraise possible biases in the selected studies.

Meta-analytic procedure

Meta-analyses were performed using Comprehensive Meta-Analysis version 4.0 (Borenstein, Hedges, Higgins, & Rothstein, 2022). Between-group (treatment *v.* control) effect sizes (Hedges' *g*) for test score changes (i.e. changes in scores on neuropsychological tests/functioning scales from baseline to a follow-up time point) were calculated as follows: (mean change treatment – mean change control)/pooled standard deviation of change. The sign of between-group effect sizes was adjusted so that positive effect sizes reflected greater improvement in the treatment group. The findings of individual RCTs were combined using a random-effects model. Whenever possible, subanalyses were performed considering only primary studies including remission (full or partial) and cognitive or functional impairment (subjectively or objectively assessed) as inclusion criteria. The *Q* test was used to explore the presence of heterogeneity among RCTs with a significance level of $p < 0.1$. Following the recommendations provided by the specialized literature (Borenstein, 2022), prediction intervals were obtained to present the extent of between-study variation. The I^2 index was calculated to describe the percentage of total variation across reports due to between-trial heterogeneity rather than by sampling error. In meta-analyses of at least five studies, sensitivity analyses were performed using the leave-one-out approach and publication bias was assessed using Egger's test. Except for the *Q* test, significance was set at $p < 0.05$ in all the analyses performed.

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Outcome measures

The results of independent RCTs were combined into summary effect sizes for different efficacy outcome measures: general functioning and six cognitive variables (online Supplementary Table S2). A meta-analysis was performed when there were at least three independent studies utilizing the same test or tapping approximately the same construct. As there is no full consensus on how individual tests map onto cognitive domains, individual-test meta-analyses were preferred and conducted whenever possible (i.e. when three independent trials using the same test were available). If a study involved more than one control group (e.g. a standard treatment group and an active control group), only the data from the best comparison group were included in the meta-analysis. In this sense, any active control condition was preferred, as the absence of psychological/behavioral treatment as a control may overestimate the effects of the psychosocial intervention explored. Given that most studies included assessment of outcome variables immediately after treatment completion and at follow-up, data obtained at different assessment timepoints were extracted separately and included in different meta-analyses.

Results

The selection process of the studies included in this review is summarized in Fig. 1. Ten RCTs met the inclusion criteria (Table 1). Seven of the selected studies were independent RCTs of CR in BD ($n = 586$). The studies by Torrent et al. (2013) and Bonnin et al. (2016b) were based on the same RCT, but the latter included long-term follow-up assessment after treatment completion. Hence, both reports were included in the quantitative synthesis but they were pooled in different meta-analyses. Subanalyses of this RCT (Bonnin et al., 2016a; Sanchez-Moreno et al., 2017; Solé et al., 2015) were not considered in the current review. As the study by Douglas et al. (2022) was based on a mixed sample of mood disorder patients, only the data for the BD subgroup were considered. The study by Tsapekos, Strawbridge, Cella, Young, and Wykes (2023) was based on the same RCT as Strawbridge et al. (2021) but included a larger sample size, despite a smaller number of cognitive domains being assessed. Therefore, only the data from the former study were included in the quantitative synthesis except in the phonemic fluency analysis, for which outcome measures were only available in the latter. As the two studies by Ott et al. (2021a, 2021b) were based on the same sample, only one (Ott et al. 2021b) was included in the meta-analysis as it provides follow-up assessment and a larger number of outcome measures. Consequently, nine studies were included in the statistical analysis but only seven were independent RCTs and could therefore be pooled together.

Study design and control conditions

All the RCTs reviewed in this study used a parallel design and, except Lewandowski et al. (2017), were single-blind. Most studies used 'treatment as usual' (TAU)/'standard care' as a control condition. Depending on the study, standard treatment could involve either prescribed pharmacological treatment without adjunctive psychosocial therapy (Bonnin et al., 2016b; Gomes et al., 2019; Torrent et al., 2013) or prescribed pharmacological treatment with some patients receiving, in addition, psychological treatment not specifically targeting cognition (Demant, Vinberg, Kessing, &

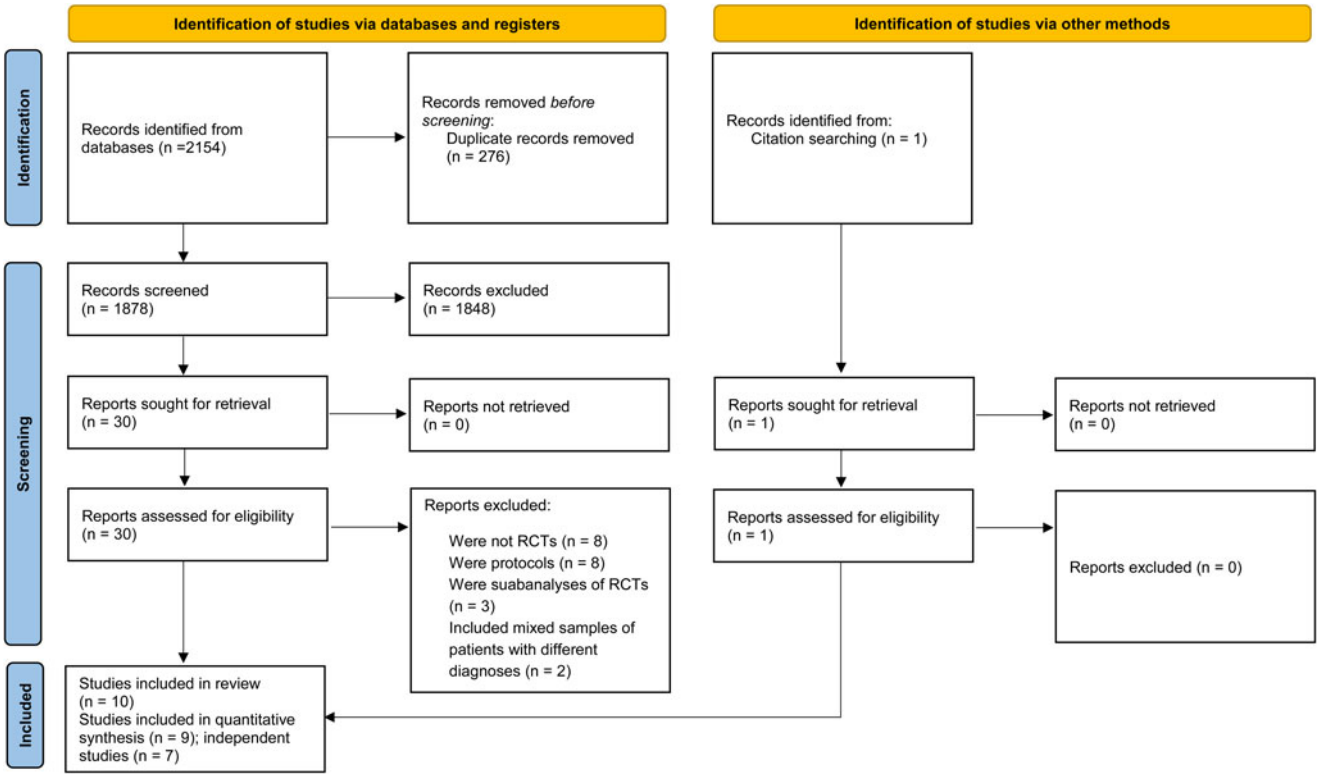

Figure 1. PRISMA 2020 flow diagram. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

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Table 1. Characteristics of the studies included in this review

Study	Design	Sample[a]	Dropouts CR/CG	Age [mean ± s.d. median (IQR)] CR/CG	Gender (% females) CR/CG	Mood state at study entry	CR intervention: duration, format, and content	Post-treatment assessment timepoints	Cognitive and functional outcome measures	Main results
Torrent et al. (2013)	Parallel Single-blind	77(CR)/82 (PSE)/80(TAU)	22/20/14	40.59 ± 9.10/ 40.47 ± 8.69	57.1%/ 57.5%	Euthymia: HDRS ⩽ 8 YMRS ⩽ 6	*Functional Remediation* 90-min group sessions delivered once a week over 21 weeks (target: 21 sessions). Neurocognitive training tackling attention, memory, and executive functions, psychoeducation on cognition-related issues, and problem solving within an ecological framework.	Week 21 (treatment completion)	Cognition: processing speed, sustained attention, executive functions (response inhibition, attentional control, working memory, planning, set shifting, verbal fluency), visual memory, verbal learning/ memory (DSST, SS, DS, SCWT, WCST, COWAT, TMT, ROCF, CVLT, LMS, LNS, CPT). Functioning (FAST).	Cognition: CR = PSE CR = TAU Functioning: CR = PSE, CR > TAU
Demant et al. (2015)	Parallel Single-blind	23(CR)/23 (TAU)	5/1	33.9 ± 6.8/34 ± 7.9	66.7%/ 59.1%	Partial or total remission: HDRS ⩽ 14 YMRS ⩽ 14	*Compensatory Cognitive Remediation* 120-min group sessions delivered once a week over 12 weeks (target: 12 sessions), and a booster session 4 weeks after treatment completion Psychoeducation and cognitive training targeting attention and concentration, memory and learning, and executive functions in everyday life.	Week 12 (treatment completion) Week 26 (follow-up assessment)	Cognition: verbal learning/memory, sustained attention, psychomotor speed, executive functions (working memory, attentional control), facial emotion recognition, and self-reported cognitive functioning (CFQ, RAVLT, TMT, DSST, DS, LNS, COWAT, and CANTAB subtests: RVP, DMS, SWM, SRT). Functioning (FAST, WSAS).	Cognition: CR > TAU Improvement in verbal fluency (week 26) Functioning: CR = TAU (weeks 12 and 26)
Bonnin et al. (2016b) Follow-up analysis of Torrent et al. (2013)	Parallel Single-blind	77(CR)/82 (PSE)/80(TAU)	23/ 22/ 22	40.59 ± 9.10/ 40.47 ± 8.69	57.1%/ 57.5%	Euthymia: HDRS ⩽ 8 YMRS ⩽ 6	*Functional Remediation* 90-min group sessions delivered once a week over 21 weeks (target: 21 sessions). Neurocognitive training tackling attention, memory, and executive functions, psychoeducation on cognition-related issues, and problem solving within an ecological framework	Week 52 (6 months after treatment completion)	Cognition: processing speed, sustained attention, executive functions (response inhibition, attentional control, working memory, planning, set shifting, verbal fluency), visual memory, verbal learning/ memory (DSST, SS, DS, SCWT, WCST, COWAT, TMT, ROCF, CVLT, LMS, LNS, CPT). Functioning (FAST).	Cognition: CR > PSE CR > TAU Improvement in verbal memory. Functioning: CR = PSE, CR > TAU

Lewandowski et al. (2017)	Parallel Double-blind	39(CR)/33 (NTCC)	18/14	29.3 ± 7.5/29.8 ± 9.2	51%/58%	Stability: cut-off scores on mood rating scales not reported.	*Neuroplasticity Informed Cognitive Remediation* 60-min individual sessions delivered approximately three times a week over 24 weeks (target: 70 sessions). Computerized training on auditory and visual perception, divided attention, memory, working memory, and problem solving.	Week 25 (treatment completion) Follow-up assessment 6 months after treatment completion.	Cognition: global cognition, processing speed, attention, working memory, verbal learning, visual learning, problem solving, and social cognition (MCCB). Functioning (MCAS).	Cognition: CR > NTCC Improvement in visual memory (at treatment completion), processing speed (at follow-up assessment) and global cognition (at both assessment timepoints). Functioning: CR = NTCC (at treatment completion and follow-up assessment)
Gomes et al. (2019)	Parallel Single-blind	31(CR)/29 (TAU)	11/10	42.7 ± 10.2/42.5 ± 10.2	80%/57.9%	Full or partial remission: MADRS ⩽ 12 YMRS ⩽ 8	*Cognitive-behavioral Rehabilitation* 90-min group sessions delivered once a week over 12 weeks (target: 12 sessions). Training on memory and attention, social cognition and communication, problem-solving strategies, and relapse prevention.	Week 13 (treatment completion)	Cognition: processing speed, executive functions (working memory, planning, attentional control), and visual memory (CANTAB battery: MOT, RVP, RTI, SSP, SWM, OTS, PRM, DMS, AST, ERT). Functioning (FAST).	Cognition: CR > TAU Improvement in reaction time, visual memory, and emotion recognition. Functioning: CR = TAU
Ott et al. (2021a)	Parallel Single-blind	32(CR)/29(GT)	6/4	36[23]/38 [22]	77%/79%	Partial or total remission: HDRS ⩽ 14 YMRS ⩽ 14	*Action-based Cognitive Remediation* 2-h group sessions delivered twice a week, with 30 min of daily computer training at home, over 10 weeks (target: 20 sessions). Computerized cognitive training, practical activities of daily living, and goal setting discussions to encourage participation in cognitively stimulating activities during daily life.	Week 11 (treatment completion)	Cognition: planning and working memory (CANTAB subtests: SWM, OTS).	Cognition: CR > GT Improvement in planning capacity

(*Continued*)

Table 1. (*Continued.*)

Study	Design	Sample[a]	Dropouts CR/CG	Age [mean ± S.D. median (IQR)] CR/CG	Gender (% females) CR/CG	Mood state at study entry	CR intervention: duration, format, and content	Post-treatment assessment timepoints	Cognitive and functional outcome measures	Main results
Ott et al. (2021b)	Parallel Single-blind	32(CR)/29(GT)	7/10	36[20]/37[22]	72%/76%	Partial or total remission: HDRS ⩽ 14 YMRS ⩽ 14	*Action-based Cognitive Remediation* 2-h group sessions delivered twice a week, with 30 min of daily computer training at home, over 10 weeks (target: 20 sessions).	Week 11 (treatment completion) Follow-up: 6 months after treatment completion	Cognition: global cognition, verbal learning/memory, processing speed, attention, and executive functions (planning, set shifting, attentional control, working memory, fluency), subjective cognitive functioning (COBRA, RAVLT, TMTb WAIS-III LNS, RBANS Coding, verbal fluency, DS, and CANTAB tests: RVP, OTS, SWM). Functioning (FAST, SDS, WSAS).	Cognition: CR > GT Improvement in planning capacity and subjective cognitive functioning (at treatment completion only) Functioning: CR = GT at both treatment completion and follow-up assessment.
Douglas et al. (2022)	Parallel Single-blind	22(CR + IPSRT)/20 (IPSRT)	4/0	38.5 ± 11.99/ 36.15 ± 14.08	77.27%/ 65%	Different mood states	*Action-based Cognitive Remediation* 20-to-30 min individual sessions integrated into weekly 60-min psychotherapy sessions, with 30-min computer training at home 3 times a week over approximately 12 weeks (target: 12 sessions). Psychoeducation about cognitive impairment in mood disorders, repeated practice of computerized cognitive exercises and strategy coaching, and discussions of transferring skills to functioning in daily life.	Month 12 (treatment completion) Month 18 (follow-up assessment)	Cognition: global cognition, psychomotor speed, attention, working memory, verbal learning/ memory, executive functions (verbal fluency, cognitive flexibility), subjective cognitive functioning (COBRA). Functioning (FAST, SAS).	Cognition: CR + IPSRT = IPSRT at both treatment completion and follow-up assessment. Functioning: CR + IPSRT < IPSRT at both treatment completion and follow-up assessment (nonsignificant trend).

Strawbridge et al. (2021)	Parallel Single-blind	29(CR)/31 (TAU)	2/5	43 [19]/42.5 [20]	72.4%/ 64.5%	Euthymia: HDRS ⩽ 7 YMRS ⩽ 7	*Computerized Interactive Remediation of Cognition – Interactive Training for Schizophrenia* Individual 60-min sessions delivered twice or three times a week over 12 weeks (target: 30-40 sessions). Training on compensatory and restorative strategies.	Week 13 (treatment completion) Week 25 (follow-up assessment)	Cognition: global cognition, psychomotor speed, attention, working memory, verbal learning/ memory, executive functions (verbal fluency and problem solving) and IQ. (DSST, SS, DS, VPA1, VPA2, COWAT, WASI). Functioning (FAST).	Cognition: CR > TAU Improvement in working memory, executive functions and IQ (weeks 13 and 25). Improvements in processing speed and verbal memory (week 25). Functioning: CR > TAU (weeks 13 and 25).
Tsapekos et al. (2023)	Parallel Single-blind	40(CR)/40 (TAU)	3/6	41.8 ± 13.9/42.6 ± 11.8	75%/67.5%	Euthymia: HDRS ⩽ 7 YMRS ⩽ 7	*Computerized Interactive Remediation of Cognition – Interactive Training for Schizophrenia* Individual 60-min sessions delivered twice or three times a week over 12 weeks (target: 30-40 sessions). Training on meta-cognition, the use of strategies and the transfer of cognitive skills to daily-life activities.	Treatment completion: week 13 Follow-up: week 25	Cognition: global cognition, psychomotor speed, attention, working memory, verbal learning/ memory, executive functions (problem solving) and IQ. (DSST, SS, DS, VPA1, VPA2, WASI). Functioning (FAST).	Cognition: CR > TAU Improvement in working memory, executive functions and IQ (weeks 13 and 25). Improvements in processing speed and verbal memory (week 25). Functioning: CR > TAU (weeks 13 and 25).

Design and interventions: CR, cognitive remediation; CG, control group; S.D., standard deviation; IPSRT, Interpersonal and Social Rhythm Therapy; IQR, interquartile range; TAU, treatment as usual; GT, group therapy; NTCC, non-therapeutic computational control; PSE, psychoeducation.
Mood assessment: HDRS, Hamilton Depression rating Scale; MADRS, Montgomery–Asberg depression rating scale; YMRS, Young Mania Rating Scale.
Objective cognitive measures: CANTAB, Cambridge Neuropsychological Test Automated Battery; COWAT, Controlled oral word association test; CPT, Continuous performance test; CVLT, California verbal learning test; DMS, Delayed matching to sample; DS, Digit span; DSST, Digit-symbol substitution test; LMS, Logical memory scale; LNS, Letter number sequencing; MCCB, Matrics Consensus Cognitive Battery; OTS, One Touch Stockings of Cambridge; RAVLT, Rey-Auditory verbal learning test; RBANS, Repeatable battery of the assessment of neuropsychological status; RBMT, Rivermead behavioral memory test; ROCF, Rey-Osterrieth Complex Figure; RVP, Rapid visual information processing; SCWT, Stroop color-word interference test; SRT, Simple reaction time; SS, Symbol search; SWM, Spatial working memory; TAP, Test of attentional performance; TMT, Trail making test; *Wechsler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence;* WCST, Wisconsin card sorting test).
Self-report cognitive measures: CFQ, Cognitive failures questionnaires; COBRA, Cognitive Complaints in Bipolar Disorder Rating Assessment.
Functional measures: FAST, Functional assessment short test; MCAS, Multnomah community ability scale; SAS, Social Adjustment Scale; SDS, Sheehan Disability Scale, WSAS, Work and social adjustment scale).
[a]Includes all patients allocated to either treatment or control arms after randomization.

Miskowiak, 2015; Strawbridge et al., 2021; Tsapekos et al., 2023). The RCT by Torrent et al. (Bonnin et al. 2016b; Torrent et al., 2013) included two comparison conditions: TAU (pharmacological treatment only) and a psychoeducation control group (psychosocial treatment with the same frequency and duration as the CR intervention in addition to prescribed pharmacological treatment).

As shown in Table 1, CR approaches were different across studies, with duration of treatment ranging between 10 and 24 weeks (weighted mean: 16 weeks). In some RCTs (Demant et al., 2015; Strawbridge et al., 2021; Tsapekos et al., 2023), many patients in the treatment (CR) group were receiving another psychological intervention not explicitly targeting cognition as part of their standard care. One RCT (Douglas et al., 2022) specifically explored the efficacy of CR in combination with another psychological treatment. Among studies including follow-up assessment after treatment completion, follow-up periods ranged between 3 and 6 months (weighted mean: 5 months) after treatment completion.

Clinical characteristics of the samples

Except the study by Douglas et al. (2022), all selected RCTs included patients in full/ partial remission at study entry. Only four studies based on two independent trials (Bonnin et al., 2016b; Strawbridge et al., 2021; Torrent et al., 2013; Tsapekos et al., 2023) considered euthymic mood state rigorously defined as an inclusion criterion. Despite all RCTs excluding patients relapsing in a serious acute mood episode throughout the study period, information on mood state at treatment completion or at follow-up assessment was not available.

Only three RCTs considered cognitive impairment subjectively (Demant et al., 2015; Douglas et al., 2022) or objectively measured (Ott et al., 2021a, 2021b) as an inclusion criterion, whereas the RCT by Torrent et al. (2013) considered the presence of moderate-to-severe functional impairment defined as a score ⩾ 18 on the Functioning Assessment Short Test (FAST) (Rosa et al., 2007) together with a score ⩾ 4 in the cognitive domain of the same scale for inclusion in the study.

Information on pharmacological variables throughout the study period of each trial was scarce. The RCT by Torrent et al. (Bonnin et al. 2016b; Torrent et al., 2013) did not provide any information about pharmacological variables but reported that treatment was kept stable in all groups throughout the study period. In the remaining RCTs, qualitative measures of exposure to medication were available, with treatment and control groups being well-balanced at baseline in terms of distribution of each class of drug (lithium, anticonvulsants, antipsychotics, antidepressants), except in the trial by Ott et al. (2021a, 2021b), in which the proportion of patients receiving antidepressants was larger in the control group without any significant between-group differences regarding other pharmacological variables. Only one trial (Gomes et al., 2019) provided the frequency distribution for medication variables at both study entry and treatment completion and no between-group differences were observed throughout the course of the study. Quantitative measures of exposure to pharmacological treatment were available only in one study (Lewandowski et al., 2017), which reported that medication did not differ by group and was essentially unchanged over the course of the study.

Risk of bias assessment

Overall, no biases were detected in the assignment of the participants to the different study groups, nor in the reporting of the results of the different investigations. However, in most trials, possible biases were found regarding the lack of blinding of the participants and the small sample size they had. Only two studies were rated as having 'high risk' of bias (Bonnin et al., 2016b; Gomes et al., 2019) (online Supplementary Table S3).

Efficacy of CR in improving general functioning

No significant effects of CR were observed on functional outcomes at treatment completion or at follow-up assessment (Tables 2 and 3, Fig. 2). The null hypothesis of homogeneity was rejected in the treatment completion meta-analyses (Table 2). The prediction interval was −0.98 to 0.90 for the General Functioning meta-analysis and −1.22 to 1.10 for the FAST-score meta-analysis. We would therefore expect that in 95% of all populations comparable to those of the analyses, the true effects will fall within these ranges. Similarly, significant heterogeneity was found in the FAST-score at follow-up meta-analysis, with a prediction interval of −0.85 to 1.15.

When meta-analyses were restricted to studies including remitted patients who were cognitively/functionally impaired at baseline (Bonnin et al., 2016b; Demant et al., 2015; Ott et al., 2021b; Torrent et al., 2013) overall effects were nonsignificant (online Supplementary Tables S4 and S5).

Table 2. Random-effects meta-analysis of CR efficacy outcomes at treatment completion

Outcome variable	No of studies	*n*	Effect size[a]	95% CI	*z*	*p*	*Q*	*Q*(*p*)	I^2	95% PI
General functioning	7	506	−0.04	−0.35 to 0.26	−0.27	0.78	16.98	0.01	64.67	−0.98 to 0.90
General functioning (FAST)[b]	6	434	−0.06	−0.42 to 0.30	−0.32	0.75	16.93	<0.01	70.48	−1.22 to 1.10
Planning	5	418	0.32	0.06–0.57	2.42	0.02	6.61	0.16	39.45	−0.36 to 1.00
Working memory	7	506	0.17	−0.01 to 0.34	1.90	0.06	3.69	0.72	0.00	_
Attentional control	4	195	−0.01	−0.29 to 0.26	−0.10	0.92	2.49	0.48	0.00	–
Phonemic fluency	5	368	0.10	−0.11 to 0.30	0.93	0.35	0.71	0.95	0.00	_
Verbal learning	5	380	0.28	−0.06 to 0.61	1.59	0.11	10.10	0.04	60.39	−0.81 to 1.37
Delayed recall	4	298	0.29	−0.12 to 0.69	1.40	0.16	7.88	0.05	61.94	−1.33 to 1.91

CI, confidence interval; CR, cognitive remediation; FAST, Functioning Assessment Short Test; PI, prediction interval.
[a]Effect sizes (Hedges'*g*) calculated as (Mean Change treatment – Mean Change control)/pooled standard deviation of change. Positive effect sizes indicate greater improvement in the CR group.
[b]Subanalysis of FAST scores.

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Table 3. Random-effects meta-analysis of CR efficacy outcomes at follow-up assessment

Outcome variable	No. of studies	*n*	Effect size[a]	95% CI	*z*	*p*	*Q*	*Q*(*p*)	I^2	95% PI
General functioning	6	354	0.14	−0.14 to 0.42	0.98	0.32	8.42	0.13	40.59	−0.60 to 0.88
General functioning (FAST)[b]	5	318	0.15	−0.17 to 0.48	0.93	0.35	8.07	0.09	50.43	−0.85 to 1.15
Planning	4	276	0.30	0.03–0.56	2.15	0.03	3.76	0.29	20.13	−0.53 to 1.13
Working memory	6	358	0.32	0.11–0.52	2.99	<0.001	4.51	0.48	0.00	–
Attentional control	4	247	−0.01	−0.25 to 0.24	−0.05	0.96	1.52	0.68	0.00	–
Phonemic fluency	5	300	0.22	0.00–0.45	1.94	0.05	1.85	0.76	0.00	–
Verbal learning	5	287	0.40	0.15–0.66	3.11	0.01	4.62	0.33	13.46	−0.13 to 0.93
Delayed recall	4	247	0.31	−0.13 to 0.74	1.37	0.17	8.28	0.04	63.79	−0.89 to 1.51

CI, confidence interval; CR, cognitive remediation; FAST, Functioning Assessment Short Test; PI, prediction interval.
[a]Effect sizes (Hedges'*g*) calculated as (Mean Change treatment – Mean Change control)/pooled standard deviation of change. Positive effect sizes indicate greater improvement in the CR group.
[b]Subanalysis of FAST scores.

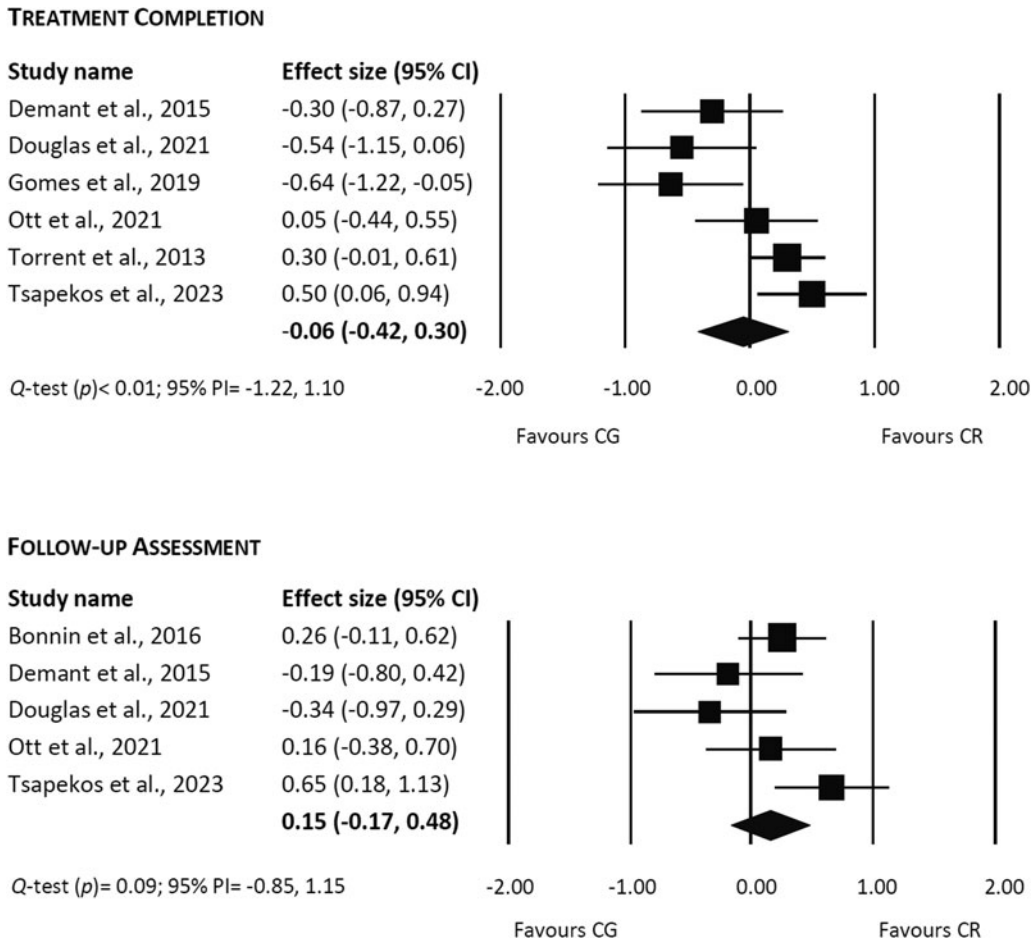

Figure 2. Random-effects meta-analysis of RCTs exploring the efficacy of CR in improving functional outcomes (reduction of FAST total scores). CG, control group; CI, confidence interval; CR, cognitive remediation; FAST, Functional Assessment Short Test; PI, prediction interval; RCT, randomized controlled trial.

No evidence of publication bias was observed (online Supplementary Table S6).

Efficacy of CR in improving cognitive functioning

Small but significant changes were observed for planning ($g = 0.32$, 95% CI 0.06–0.57) at treatment completion (Table 2). At follow-up assessment, significant effects of CR were observed for planning ($g = 0.30$, 95% CI 0.03–0.56), working memory ($g = 0.32$, 95% CI 0.11–0.52), and list learning ($g = 0.40$, 95% CI 0.15–0.66) (Table 3). No significant effects were found for the remaining neuropsychological variables analyzed. The hypothesis of homogeneity of effect sizes was rejected in the list learning meta-analysis at treatment completion and in the delayed recall

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meta-analysis at treatment completion and follow-up assessment (Tables 2 and 3).

When meta-analyses were restricted to studies including remitted patients who were cognitively/functionally impaired at baseline (Bonnin et al., 2016b; Demant et al., 2015; Ott et al., 2021b; Torrent et al., 2013), nonsignificant effects were found (online Supplementary Tables S4 and S5).

No evidence of publication bias was observed (online Supplementary Table S6).

Sensitivity analysis

Online Supplementary Figure S1 displays the effect of removing every single study on the overall estimates. For general functioning at treatment completion and follow-up assessment, results remained nonsignificant when removing any of the RCTs, thus supporting the robustness of the overall outcome measure. For the cognitive variables explored, most overall effects did not vary substantially when removing any of the studies from the synthesis except in two variables: planning and working memory at treatment completion. In the former, the removal of Ott et al. (2021b) or Tsapekos et al. (2023) rendered the observed effects nonsignificant, and similarly did the removal of either of two studies (Gomes et al., 2019; Lewandowski et al., 2017) in the latter variable. Interestingly, the removal of Douglas et al. (2022), which is the only study including patients with different mood states and exploring a combination of psychological treatments, did not change the overall effects. Similarly, the exclusion of Torrent et al. (2013)/Bonnin et al. (2016b), which used a different CR approach, did not change the overall outcome.

Discussion

The current study is the first to explore the efficacy of CR in BD by means of meta-analytic procedures and provides an updated synthesis of the best available evidence on this topic. Ten RCTs reporting the findings of seven independent trials were reviewed. At the primary study level, most reports did not show any significant effects of CR on general functioning and none of the RCTs including an active control group as comparison has demonstrated superiority of CR in improving general functioning. As regards cognitive outcomes, most studies reported significant effects of CR on at least one neuropsychological domain. The efficacy of CR on functional outcomes and six neurocognitive variables (working memory, attentional control, planning, phonemic fluency, list learning, and delayed recall) was explored at treatment completion and after follow-up. Small but significant effect sizes were observed for list learning, planning, and working memory. However, overall effects of CR on general functioning were nonsignificant at both treatment completion and follow-up assessment.

The results of this review contrast with findings in the field of schizophrenia spectrum disorders, where different meta-analyses have shown that CR exerts a significant though small improvement in the functional outcomes of those affected (Kambeitz-Ilankovic et al., 2019; Lejeune et al., 2021; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). In addition, the effects of CR have been shown to be long-lasting and may be increased when CR is combined with other psychological treatments (Kambeitz-Ilankovic et al., 2019; Wykes et al., 2011). Contrarily, in BD patients, the small effects observed for cognitive variables did not translate into a better overall functioning. These outcomes could be partially explained by the neuropsychological differences that exist between disorders. Conspicuous neuropsychological impairment is mainly related to mood symptoms in BD, whereas in schizophrenia, this is a more persistent feature. In addition, cognitive impairment is more severe and generalized in schizophrenia, affecting areas such as social cognition and fluid intelligence, which are preserved in most BD patients (Martino, Samamé, & Strejilevich, 2017; Samamé, 2019). Indeed, in schizophrenia patients, social cognition predicts community outcomes better than non-social cognitive domains (Fett et al., 2011), thus reflecting a distinct pattern of impairment between these disorders. Further, only about 20% of people affected by BD exhibit a magnitude of neuropsychological impairment similar to that observed in schizophrenia and approximately 30% do not present with measurable cognitive deficits (Burdick et al., 2014; Ehrlich et al., 2022). Therefore, it is possible that this conspicuous heterogeneity obscures stronger effects of CR occurring in the most impaired subgroup of BD patients. Finally, it has been shown that people affected by BD are more vulnerable to extrapyramidal effects of antipsychotics than those affected by schizophrenia (Gao et al., 2008). It is therefore logical to suppose that this vulnerability could extend to the cognitive adverse effects of these drugs and consequently overshadow the effects of CR among BD patients treated with antipsychotics.

A number of clinical and research considerations arise from the results of this study. First, the finding of a nonsignificant effect of CR on functional outcomes does not support the inclusion of these interventions as recommended treatments for BD in clinical guidelines for the management of the disorder. It is worth remembering that psychosocial interventions are not free from negative effects as an excessive or unnecessary exposure to the health system may be detrimental to patients (Samamé, 2021). For instance, CR implies significant direct and indirect costs that should be considered, as it not only involves specialized human resources but also requires patients to travel to clinical care centers, with the consequent time and economic costs.

These considerations are particularly relevant as CR approaches have been emphatically proposed in recent years as interventions that should be delivered to address specific cognitive deficits during different 'stages' of illness with the aim of arresting the effects of neuroprogression (Montejo et al., 2022; Torrent et al., 2013). At present, the evidence for the efficacy of RC derives mainly from small non RCTs (Bellani et al., 2019). Further, the hypothesis of neuroprogression is not supported by a recent meta-analysis (Samamé, Cattaneo, Richaud, Strejilevich, & Aprahamian, 2022) of controlled long-term studies (mean weighted follow-up: 8.9 years) and neurocognitive outcomes in late-life BD patients (Montejo et al., 2022; Samamé, Martino, & Strejilevich, 2013). In addition, BD may not be a 'stageable' condition as there is no one single 'bipolar-specific' process subserving the disorder (Malhi & Bell, 2021; Samamé, 2023).

Second, given that no pro-cognitive treatment has proven efficacious in BD and, taking into account that suboptimal cognitive performance is one of the main correlates of poor functional adjustment, clinicians should make their biggest efforts to explore and manage variables with a deleterious impact on cognition. Some of these variables may be the effects of prolonged or excessive use of some medications such as antipsychotics, which have been shown to be related to abnormalities in brain volume and diminished cognitive functioning in BD and other psychiatric disorders (Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005; Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011;

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Kanahara, Yamanaka, Shiko, Kawasaki, & Iyo, 2022; Voineskos et al., 2020). Further, cardiovascular and metabolic risk factors have been shown to be increased among BD patients and require adequate management to prevent cognitive and functional disabilities as well as premature death (Crump, Sundquist, Winkleby, & Sundquist, 2013; Rossom, Hooker, O'Connor, Crain, & Sperl-Hillen, 2022). Other variables related to treatment that could affect cognition such as lithium-related hypothyroidism should be controlled to optimize cognitive and functional outcomes (Strejilevich, Samamé, & Martino, 2015). In addition, clinicians should prioritize the use of drugs with a more benign profile of cognitive effects such as lithium (Burdick et al., 2020).

Finally, the broad heterogeneity that exists among BD patients should not be overlooked. For this reason, although CR may not be an efficacious approach to the management of BD patients 'as a group', a subgroup of patients with specific cognitive features, and in the absence of 'secondary' causes of cognitive impairment, could benefit from specific CR treatments. Indeed, though the significant effect observed for some cognitive variables does not transfer into functional outcomes in this meta-analysis, findings from individual studies (Tsapekos et al., 2023) show that improvement in global cognition accounts for more than one third of the CR effect on psychosocial functioning, thus providing support for the theoretical model of CR. Of note, however, in this study, negative results were also found when considering only studies of cognitively/functionally impaired remitted patients.

Limitations

The results of this review should be interpreted cautiously due to some limitations. First, a small number of studies were included, which are all the RCTs published to date. Further, due to the scarcity of available data, only a few cognitive and functioning variables could be analyzed and it was not possible to perform further analyses to explore the heterogeneity observed in some meta-analyses. In addition, CR interventions were very diverse across studies regarding their content, number of sessions, and schedule, and it is possible that a significant effect emerges from certain variants of CR applied to patients with specific cognitive features.

Other limitations, however, are those of the individual studies, although most of the RCTs included in the quantitative synthesis did not have a high risk of bias. Sample sizes were relatively small and high attrition rates were observed (between 11% and 44%). Hence, in the absence of intent-to-treat analyses in most studies, it is possible that the effects of CR on different outcome measures were overestimated. In addition, none of the studies examined participant satisfaction in relation to treatment outcomes. Practice effects for neuropsychological testing cannot be ruled out, particularly for trials with a short follow-up period. Other limitation was the lack of objective reports of cognitive dysfunction as an inclusion criterion in most studies and the inclusion of 'treatment as usual' as a control condition rather than an active control. Furthermore, it is worth noting that double blinding is hardly possible to accomplish in RCTs of psychosocial treatments, which can lead to biased findings.

Another major shortcoming regards mood state during trials. Patients with partial remission were included in most trials as recommended by experts in the field (Miskowiak, Carvalho, Vieta, & Kessing, 2016) under the assumption that this criterion would render BD samples more representative. Further, mood changes throughout study periods were not controlled in most trials. It is evident that the impact of subsyndromal symptoms on cognition cannot be overlooked, and mood fluctuations at study entry and along the course of the RCTs could be either masking or overestimating the effects of CR. Indeed, Bonnin et al. (2016b) reported that between-arm differences regarding changes in the FAST total score were no longer significant after controlling for subthreshold depressive symptoms at six-month follow-up assessment. Finally, the effects of pharmacological treatment should be considered as these may improve or impair cognitive outcomes, and information regarding dose of each class of medication and changes across study periods were not available for most trials. One study (Lewandowski et al., 2017), however, adjusted the results for pharmacological variables (lithium and antipsychotics dose), and the inclusion of these covariates did not change the observed findings.

Conclusions

Although CR could exert a positive effect on some domains of executive functioning and verbal memory among BD patients, there is no robust evidence supporting that this effect translates into an improvement at the functional level. However, these results are preliminary and should be interpreted cautiously. Future lines of research should continue to explore the efficacy of different CR approaches in BD, using experimental designs (RCTs), with larger sample size, enriched samples, active control groups, and a more thorough control of mood, metabolic, and pharmacological variables together with other factors that could modulate cognitive performance. In addition, in order to base treatment recommendations on more robust pieces of evidence, it is important that future guidelines provide a clear definition for the 'gold standard' of RCTs of psychosocial interventions as regards blinding and control conditions. Finally, future studies should compare the efficacy of CR with that of other activities that can be conducted in the community and without added professional costs, such as sports or recreational activities. In the meantime, there is no sufficient evidence to recommend CR among the main psychosocial treatments for the management of BD.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001897

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Data availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Bellani, M., Biagianti, B., Zovetti, N., Rossetti, M. G., Bressi, C., Perlini, C., & Brambilla, P. (2019). The effects of cognitive remediation on cognitive abilities and real-world functioning among people with bipolar disorder: A

systematic review: Special section on "Translational and Neuroscience Studies in Affective Disorders". Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summaries relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders. *Journal of Affective Disorders*, *257*, 691–697. doi: 10.1016/j.jad.2019.07.059

Bonnin, C. M., Reinares, M., Martínez-Arán, A., Balanzá-Martínez, V., Sole, B., Torrent, C., … CIBERSAM Functional Remediation Group (2016a). Effects of functional remediation on neurocognitively impaired bipolar patients: Enhancement of verbal memory. *Psychological Medicine*, *46*(2), 291–301. doi: 10.1017/S0033291715001713

Bonnin, C. M., Torrent, C., Arango, C., Amann, B. L., Solé, B., González-Pinto, A., … CIBERSAM Functional Remediation Group (2016b). Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. *The British Journal of Psychiatry: the Journal of Mental Science*, *208*(1), 87–93. doi: 10.1192/bjp.bp.114.162123

Borenstein, M. (2022). In a meta-analysis, the I-squared statistic does not tell us how much the effect size varies. *Journal of Clinical Epidemiology*, *152*, 281–284. doi: 10.1016/j.jclinepi.2022.10.003

Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2022). *Comprehensive meta-analysis, version 4*. Englewood, NJ: Biostat.

Burdick, K. E., Millett, C. E., Russo, M., Alda, M., Alliey-Rodriguez, N., Anand, A., … Kelsoe, J. R. (2020). The association between lithium use and neurocognitive performance in patients with bipolar disorder. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *45*(10), 1743–1749. doi: 10.1038/s41386-020-0683-2

Burdick, K. E., Russo, M., Frangou, S., Mahon, K., Braga, R. J., Shanahan, M., & Malhotra, A. K. (2014). Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: Clinical implications. *Psychological Medicine*, *44*(14), 3083–3096. doi: 10.1017/S0033291714000439

Crump, C., Sundquist, K., Winkleby, M. A., & Sundquist, J. (2013). Comorbidities and mortality in bipolar disorder: A Swedish national cohort study. *JAMA Psychiatry*, *70*(9), 931–939. doi: 10.1001/jamapsychiatry.2013.1394

Demant, K. M., Vinberg, M., Kessing, L. V., & Miskowiak, K. W. (2015). Effects of short-term cognitive remediation on cognitive dysfunction in partially or fully remitted individuals with bipolar disorder: Results of a randomised controlled trial. *PloS One*, *10*(6), e0127955. doi: 10.1371/journal.pone.0127955

Douglas, K. M., Groves, S., Crowe, M. T., Inder, M. L., Jordan, J., Carlyle, D., … Porter, R. J. (2022). A randomised controlled trial of psychotherapy and cognitive remediation to target cognition in mood disorders. *Acta Psychiatrica Scandinavica*, *145*(3), 278–292. doi: 10.1111/acps.13387

Ehrlich, T. J., Ryan, K. A., Burdick, K. E., Langenecker, S. A., McInnis, M. G., & Marshall, D. F. (2022). Cognitive subgroups and their longitudinal trajectories in bipolar disorder. *Acta Psychiatrica Scandinavica*, *146*(3), 240–250. doi: 10.1111/acps.13460

Ehrminger, M., Brunet-Gouet, E., Cannavo, A. S., Aouizerate, B., Cussac, I., Azorin, J. M., … Roux, P. (2021). Longitudinal relationships between cognition and functioning over 2 years in euthymic patients with bipolar disorder: A cross-lagged panel model approach with the FACE-BD cohort. *The British Journal of Psychiatry: the Journal of Mental Science*, *218*(2), 80–87. doi: 10.1192/bjp.2019.180

Fett, A. K., Viechtbauer, W., Dominguez, M. D., Penn, D. L., van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, *35*(3), 573–588. doi: 10.1016/j.neubiorev.2010.07.001

Frangou, S., Donaldson, S., Hadjulis, M., Landau, S., & Goldstein, L. H. (2005). The Maudsley bipolar disorder project: Executive dysfunction in bipolar disorder I and its clinical correlates. *Biological Psychiatry*, *58*(11), 859–864. doi: 10.1016/j.biopsych.2005.04.056

Gao, K., Kemp, D. E., Ganocy, S. J., Gajwani, P., Xia, G., & Calabrese, J. R. (2008). Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: A systematic review. *Journal of Clinical Psychopharmacology*, *28*(2), 203–209. doi: 10.1097/JCP.0b013e318166c4d5

Gitlin, M. J., & Miklowitz, D. J. (2017). The difficult lives of individuals with bipolar disorder: A review of functional outcomes and their implications for treatment. *Journal of Affective Disorders*, *209*, 147–154. doi: 10.1016/j.jad.2016.11.021

Gomes, B. C., Rocca, C. C., Belizario, G. O., de B F Fernandes, F., Valois, I., Olmo, G. C., … Lafer, B. (2019). Cognitive behavioral rehabilitation for bipolar disorder patients: A randomized controlled trial. *Bipolar Disorders*, *21*(7), 621–633. doi: 10.1111/bdi.12784

Ho, B. C., Andreasen, N. C., Ziebell, S., Pierson, R., & Magnotta, V. (2011). Long-term antipsychotic treatment and brain volumes: A longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry*, *68*(2), 128–137. doi: 10.1001/archgenpsychiatry.2010.199

Jones, B. D. M., Fernandes, B. S., Husain, M. I., Ortiz, A., Rajji, T. K., Blumberger, D. M., … Mulsant, B. H. (2022). A cross-sectional study of cognitive performance in bipolar disorder across the lifespan: The cog-BD project. *Psychological Medicine*, 1–9. Advance online publication. doi: 10.1017/S0033291722003622

Kambeitz-Ilankovic, L., Betz, L. T., Dominke, C., Haas, S. S., Subramaniam, K., Fisher, M., … Kambeitz, J. (2019). Multi-outcome meta-analysis (MOMA) of cognitive remediation in schizophrenia: Revisiting the relevance of human coaching and elucidating interplay between multiple outcomes. *Neuroscience and Biobehavioral Reviews*, *107*, 828–845. doi: 10.1016/j.neubiorev.2019.09.031

Kanahara, N., Yamanaka, H., Shiko, Y., Kawasaki, Y., & Iyo, M. (2022). The effects of cumulative antipsychotic dose on brain structures in patients with schizophrenia: Observational study of multiple CT scans over a long-term clinical course. *Psychiatry Research. Neuroimaging*, *319*, 111422. doi: 10.1016/j.pscychresns.2021.111422

Keramatian, K., Torres, I. J., & Yatham, L. N. (2022). Neurocognitive functioning in bipolar disorder: What we know and what we don't. *Dialogues in Clinical Neuroscience*, *23*(1), 29–38. doi: 10.1080/19585969.2022.2042164

Lejeune, J. A., Northrop, A., & Kurtz, M. M. (2021). A meta-analysis of cognitive remediation for schizophrenia: Efficacy and the role of participant and treatment factors. *Schizophrenia Bulletin*, *47*(4), 997–1006. doi: 10.1093/schbul/sbab022

Lewandowski, K. E., Sperry, S. H., Cohen, B. M., Norris, L. A., Fitzmaurice, G. M., Ongur, D., & Keshavan, M. S. (2017). Treatment to Enhance Cognition in Bipolar Disorder (TREC-BD): Efficacy of a randomized controlled trial of cognitive remediation versus active control. *The Journal of Clinical Psychiatry*, *78*(9), e1242–e1249. doi: 10.4088/JCP.17m11476

Malhi, G. S., & Bell, E. (2021). Questions in Psychiatry (QuiP): Is staging bipolar disorder possible? If so, where to begin? *Bipolar Disorders*, *23*(5), 517–520. doi: 10.1111/bdi.13103

Malhi, G. S., Bell, E., Boyce, P., Bassett, D., Berk, M., Bryant, R., … Murray, G. (2020). The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: Bipolar disorder summary. *Bipolar Disorders*, *22*(8), 805–821. doi: 10.1111/bdi.13036

Martino, D. J., Samamé, C., & Strejilevich, S. A. (2017). Social cognition in schizophrenia and bipolar disorder: Just quantitative differences..?. *Schizophrenia Research*, *183*, 164–165. doi: 10.1016/j.schres.2016.11.023

Mignogna, K. M., & Goes, F. S. (2022). Characterizing the longitudinal course of symptoms and functioning in bipolar disorder. *Psychological Medicine*, 1–11. Advance online publication. doi: 10.1017/S0033291722001489

Miskowiak, K. W., Burdick, K. E., Martinez-Aran, A., Bonnin, C. M., Bowie, C. R., Carvalho, A. F., … Vieta, E. (2018). Assessing and addressing cognitive impairment in bipolar disorder: The international society for bipolar disorders targeting cognition task force recommendations for clinicians. *Bipolar Disorders*, *20*(3), 184–194. doi: 10.1111/bdi.12595

Miskowiak, K. W., Carvalho, A. F., Vieta, E., & Kessing, L. V. (2016). Cognitive enhancement treatments for bipolar disorder: A systematic review and methodological recommendations. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *26*(10), 1541–1561. doi: 10.1016/j.euroneuro.2016.08.011

Miskowiak, K. W., Seeberg, I., Jensen, M. B., Balanzá-Martínez, V., Del Mar Bonnin, C., Bowie, C. R., … Vieta, E. (2022). Randomised controlled cognition trials in remitted patients with mood disorders published between 2015 and 2021: A systematic review by the international society for bipolar disorders targeting cognition task force. *Bipolar Disorders*, *24*(4), 354–374. doi: 10.1111/bdi.13193

Montejo, L., Torrent, C., Jiménez, E., Martínez-Arán, A., Blumberg, H. P., Burdick, K. E., … International Society for Bipolar Disorders (ISBD) Older Adults with Bipolar Disorder (OABD) Task Force. (2022). Cognition in older adults with bipolar disorder: An ISBD task force systematic review and meta-analysis based on a comprehensive neuropsychological assessment. *Bipolar Disorders*, *24*(2), 115–136. doi: 10.1111/bdi.13175

Ott, C. V., Macoveanu, J., Bowie, C. R., Fisher, P. M., Knudsen, G. M., Kessing, L. V., & Miskowiak, K. W. (2021a). Change in prefrontal activity and executive functions after action-based cognitive remediation in bipolar disorder: A randomized controlled trial. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*, *46*(6), 1113–1121. doi: 10.1038/s41386-020-00901-7

Ott, C. V., Vinberg, M., Kessing, L. V., Bowie, C. R., Forman, J. L., & Miskowiak, K. W. (2021b). Effect of action-based cognitive remediation on cognitive impairment in patients with remitted bipolar disorder: A randomized controlled trial. *Bipolar Disorders*, *23*(5), 487–499. doi: 10.1111/bdi.13021

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* (*Clinical Research ed.*), *372*, n71. doi: 10.1136/bmj.n71

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., & Moore, P. B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders*, *93*(1-3), 105–115. doi: 10.1016/j.jad.2006.02.016

Rosa, A. R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., … Vieta, E. (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health: CP & EMH*, *3*, 5. doi: 10.1186/1745-0179-3-5

Rossom, R. C., Hooker, S. A., O'Connor, P. J., Crain, A. L., & Sperl-Hillen, J. M. (2022). Cardiovascular risk for patients with and without schizophrenia, schizoaffective disorder, or bipolar disorder. *Journal of the American Heart Association*, *11*(6), e021444. doi: 10.1161/JAHA.121.021444

Samamé, C. (2019). The role of fluid intelligence in ascertaining neuropsychological and functional differences between bipolar disorder and primary psychotic disorders. *Bipolar Disorders*, *21*(5), 462. doi: 10.1111/bdi.12791

Samamé, C. (2021). The rise and fall of cognitive-behavioral approaches to the treatment of bipolar disorder: A critical overview from a quaternary prevention perspective. *Bipolar Disorders*, *23*(8), 751–753. doi: 10.1111/bdi.13146

Samamé, C. (2023). Progressive cognitive impairment in bipolar disorder: An assumption that holds true no matter what. *Bipolar Disorders*, *25*(1), 82. doi: 10.1111/bdi.13289

Samamé, C., Cattaneo, B. L., Richaud, M. C., Strejilevich, S., & Aprahamian, I. (2022). The long-term course of cognition in bipolar disorder: A systematic review and meta-analysis of patient-control differences in test-score changes. *Psychological Medicine*, *52*(2), 217–228. doi: 10.1017/S0033291721004517

Samamé, C., Martino, D. J., & Strejilevich, S. A. (2013). A quantitative review of neurocognition in euthymic late-life bipolar disorder. *Bipolar Disorders*, *15*(6), 633–644. doi: 10.1111/bdi.12077

Sanchez-Moreno, J., Bonnín, C., González-Pinto, A., Amann, B. L., Solé, B., Balanzá-Martínez, V., … CIBERSAM Functional Remediation Group. (2017). Do patients with bipolar disorder and subsyndromal symptoms benefit from functional remediation? A 12-month follow-up study. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *27*(4), 350–359. doi: 10.1016/j.euroneuro.2017.01.010

Solé, B., Bonnin, C. M., Mayoral, M., Amann, B. L., Torres, I., González-Pinto, A., … CIBERSAM Functional Remediation Group. (2015). Functional remediation for patients with bipolar II disorder: Improvement of functioning and subsyndromal symptoms. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *25*(2), 257–264. doi: 10.1016/j.euroneuro.2014.05.010

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., … Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* (*Clinical research ed.*), *366*, l4898. doi: 10.1136/bmj.l4898

Strawbridge, R., Tsapekos, D., Hodsoll, J., Mantingh, T., Yalin, N., McCrone, P., … Young, A. H. (2021). Cognitive remediation therapy for patients with bipolar disorder: A randomised proof-of-concept trial. *Bipolar Disorders*, *23*(2), 196–208. doi: 10.1111/bdi.12968

Strejilevich, S. A., Samamé, C., & Martino, D. J. (2015). The trajectory of neuropsychological dysfunctions in bipolar disorders: A critical examination of a hypothesis. *Journal of Affective Disorders*, *175*, 396–402. doi: 10.1016/j.jad.2015.01.018

Tamura, J. K., Carvalho, I. P., Leanna, L. M. W., Feng, J. N., Rosenblat, J. D., Mansur, R., … McIntyre, R. S. (2021). Management of cognitive impairment in bipolar disorder: A systematic review of randomized controlled trials. *CNS Spectrums*, 1–22. Advance online publication. doi: 10.1017/S1092852921000092

Torrent, C., Bonnin, C. d., Martínez-Arán, A., Valle, J., Amann, B. L., González-Pinto, A., … Vieta, E. (2013). Efficacy of functional remediation in bipolar disorder: A multicenter randomized controlled study. *The American Journal of Psychiatry*, *170*(8), 852–859. doi: 10.1176/appi.ajp.2012.12070971

Tsapekos, D., Seccomandi, B., Mantingh, T., Cella, M., Wykes, T., & Young, A. H. (2020). Cognitive enhancement interventions for people with bipolar disorder: A systematic review of methodological quality, treatment approaches, and outcomes. *Bipolar Disorders*, *22*(3), 216–230. doi: 10.1111/bdi.12848

Tsapekos, D., Strawbridge, R., Cella, M., Wykes, T., & Young, A. H. (2021). Predictors of psychosocial functioning in euthymic patients with bipolar disorder: A model selection approach. *Journal of Psychiatric Research*, *143*, 60–67. doi: 10.1016/j.jpsychires.2021.08.013

Tsapekos, D., Strawbridge, R., Cella, M., Young, A. H., & Wykes, T. (2023). Does cognitive improvement translate into functional changes? Exploring the transfer mechanisms of cognitive remediation therapy for euthymic people with bipolar disorder. *Psychological Medicine*, *53*(3), 936–944. doi: 10.1017/S0033291721002336

Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., & Wykes, T. (2021). Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: A systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*, *78*(8), 848–858. doi: 10.1001/jamapsychiatry.2021.0620

Voineskos, A. N., Mulsant, B. H., Dickie, E. W., Neufeld, N. H., Rothschild, A. J., Whyte, E. M., … Flint, A. J. (2020). Effects of antipsychotic medication on brain structure in patients with major depressive disorder and psychotic features: Neuroimaging findings in the context of a randomized placebo-controlled clinical trial. *JAMA Psychiatry*, *77*(7), 674–683. doi: 10.1001/jamapsychiatry.2020.0036

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. *The American Journal of Psychiatry*, *168*(5), 472–485. doi: 10.1176/appi.ajp.2010.10060855

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., … Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders*, *20*(2), 97–170. doi: 10.1111/bdi.12609