

THE EFFECTS OF COGNITIVE REMEDIATION THERAPY IN BIPOLAR DISORDER PATIENTS

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REVIEW

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ABSTRACT

Background: Bipolar Disorder (BD) is a mental disorder impacting 45 million people worldwide. BD patients often experience persistent cognitive impairments. These cognitive impairments can impact psychosocial outcomes and reduce employment. Cognitive remediation (CR) is a behavioral training-based intervention that points to help cognitive processes and improve functional outcomes. The effects of CR in BD are inconclusive. Some studies claimed that CR could improve many cognitive domains and increase Quality of Life, but other study claims that CR didn't improve overall cognitive and psychosocial functioning. In this paper, we aim to explore the effect of CR in BD patients.

Objective: To understand the effects of cognitive remediation therapy in bipolar disorder patients.

Methods: The author tried to explore all the papers in English published from 2018 to 2022. The electronic databases used are Google Scholar, ScienceDirect, Elsevier, Wiley Library, PubMed, and Cochrane. Two sets of keyword search algorithms were used with Boolean operator AND. The first keyword was "bipolar disorder" and the second was "cognitive remediation". Then we included all publications that covered the effects of CR in BD.

Results: Involvement all cognitive domains need to be evaluate first before bring cognitive remediation therapy. Follow up on their quality of life, function memory recall and brain function, event the patient can still need to be evaluate with antipsychotic or mood stabilizer drugs..

Conclusion: CR has some effects in BD patients related to multiple cognitive domains (global cognition, executive function, attention, learning, and memory), IQ, psychosocial functions, functional outcomes, and goal attainment. More high-quality randomized trials with objective cognitive impairments as inclusion criteria of the participants, the longer intervention of CR, better control of biases, language and perceptual-motor function observed, and bigger sample size are required.

Keywords: cognitive function, cognitive remediation, bipolar disorder.

Article History:

Received: March 7, 2022

Accepted: April 5, 2022

Published: September 30, 2022

Cite this as: Astami, C.P. The effects of cognitive remediation therapy in bipolar disorder patients. *Journal of Psychiatry Psychology and Behavioral Research*; 2022;3:2. p36-42.

INTRODUCTION

Bipolar Disorder (BD) is a mental disorder represented by recurrent episodes of mania/hypomania and depression, impacting 45 million people worldwide.¹ Not only causing affective impairments, bipolar disorder (BD) patients often experience persistent cognitive impairments. Some cognitive domains affected are especially related to executive function, verbal memory and learning, and attention, and this occurred even during remission or euthymia.^{2,3} These cognitive impairments can impact psychosocial outcomes and reduce employment⁴. These also affect occupational function more than residual depressive symptoms.⁵ The episode recurrence can be more frequent if cognitive impairments present, so improving cognitive abilities might enhance not only short-term function but also the long-term.⁶

Despite the increasing number of negative psychosocial and occupational cognitive effects in BD patients, there is currently no effective management with direct and long effects on cognition. Pharmacological treatment has shown no efficacy.⁷ Non-pharmacological treatment that was recently thought to be able in managing cognitive symptoms is cognitive remediation therapy (CR). CR is a behavioral training-based intervention that points to help cognitive processes (social cognition, verbal memory, executive function, attention, and metacognition) and to improve functional outcomes.⁸ The effects of CR in BD are inconclusive. Some studies claimed that CR could improve many cognitive domains, such as verbal fluency, subjective mental acuity, executive functioning, psychosocial functioning, and occupational functioning. CR could also increase Quality of Life and decrease depressive symptoms.^{9,10,11} And even in the psychosis phase, CR improved processing speed, visual learning and memory, and

global cognition.¹² In contrast with another study, overall cognitive and psychosocial functioning in individuals with BD in full or partial remission does not appear to improve the following CR.⁵ However, the study sample size was small and it was unclear whether the participants had neurocognitive dysfunction at baseline. In this paper, we aim to explore the effect of CR in BD patients. As we know, currently no study reviews the same topics that include the latest research from 2018.

METHOD

We tried to explore all the papers in English published from 2018 to 2022. The electronic databases used are Google Scholar, ScienceDirect, Elsevier, Wiley Library, PubMed, and Cochrane. Two sets of keyword search algorithms were used with the Boolean operator AND. The first keyword was "bipolar disorder" and the second was "cognitive remediation". Then we included all publications that covered the effects of CR in BD.

RESULT AND DISCUSS

Cognitive Remediation Therapy

Cognition is a vital factor that influences the quality of life and everyday functioning. In DSM-5, the six main cognitive domains are attention, executive function, learning, and memory, language, perceptual-motor, and social cognition. Every domain consists of some sub-domains. For attention, the sub-domains are basic attention span, sustained attention, divided attention, selective attention, and processing speed. For executive function, the sub-domains are planning and decision making, working memory, responding to feedback, inhibition, and flexibility. For learning and memory, the sub-domains are immediate memory; recent memory: free recall, cued recall, recognition memory; semantic and autobiographical long-term memory; implicit learning; and spatial memory. For language, the sub-domains are expressive language and receptive language. For perceptual-motor, the sub-domains are visual perception, visuo-constructional reasoning, and perceptual-motor coordination. And lastly, for social cognition, the sub-domains are recognition of emotions, theory of mind, insight, and attributional style.¹³

Cognitive remediation (CR) is a behavioral training-based intervention that points to help cognitive processes and facilitate functional recovery.⁸ CR has been widely used in treating mental illnesses in which cognitive impairment is present, such as in schizophrenia, ADHD, substance use disorders, autism spectrum disorder, anorexia nervosa, social anxiety disorder, and BD.¹³ The definition of CR by the Cognitive Remediation Expert Working Group (CREW) in 2012 is an intervention targeting cognitive deficit (attention, memory, executive function, social cognition, or metacognition) using scientific principles of learning with the ultimate goal of improving functional outcomes. It should be noted that CR is a broad-based term that can be used to refer any methods to improve cognitive symptoms, so it presents in a variety of ways.¹⁴ CR can also be done individually or in groups, non-computer or computer-based, and the number of training sessions can vary by program.¹³ Intensive and longer duration individual CR might demonstrate better benefits.⁶ Demant et al. designed a CR program that has been followed by many subsequent researchers. CR duration is 12 weeks with 2 hours per session. The program consists of psychoeducation

and individual identification of cognitive impairments in BD and training (either directly or using the RehaCom computer program). The 12 sessions consist of 2 sessions of introduction, 3 sessions of attention and concentration (eg mindfulness meditation), 3 sessions of memory and learning (eg reading a newspaper for 10 minutes then telling each other about the topics, break for 15 minutes, then recalling what they have discussed; memory techniques including reading aloud, taking brief notes and using visual imagery, and using digital calendar); 4 sessions of executive function (discussing an individual daily-task problem they face in a group and try to make creative solutions).¹⁵

One example of computerized CR is the web-based program CIRCuiTs. This program has been widely approved and used by clients, and has a high level of satisfaction. With CIRCuiTs, patients are taught various cognitive strategies to help them improve their abilities such as memory, planning, and concentration. In the program there is a virtual village and the patient will have several tasks in each building. There are 27 tasks with 12 difficulty levels. Tasks are divided into "abstract tasks" and "exercises". Abstract tasks using numbers or geometric shapes. Exercises are more complex than abstract tasks, which involve multiple cognitive domains, especially executive functions. Exercise is divided into work, social situations, cooking, shopping, and traveling. In each session, the therapist will help patients evaluate and implement what they get from CIRCuiTs into their daily lives.^{16,17}

Another type of CR is ABCR (Action-Based Cognitive Remediation Therapy). ABCR was developed in Canada, involving 4-6 participants and two therapists, lasted for 10 weeks with a frequency of twice a week for 2 hours. The program covers the following cognitive domains: meta-cognition, verbal and visual working memory, memory, attention, and executive functions. Participants were given daily homework such as organizing documents, reading, planning a meal, scheduling appointments, remembering new people's names, making a budget, and other everyday tasks. This program also used the computer program HappyNeuron Pro.¹⁸

Cognitive Impairment in Bipolar Disorder

Objective cognitive impairments are present even in remitted or subsyndromal phase BD.¹⁹ Two-thirds of BD patients have attention, spanning memory, and executive functions impairments in the remission period.^{4,20} Cullen et al. in their systematic review study about the prevalence of cognitive impairment in remission BD adults, and the prevalence in every domain are visual memory 11.5–32.9%; speed-sensitive executive function 10.0–36.8%; speed/reaction time 23.3–44.2%; verbal memory 8.2–42.1%; attention/working memory 9.6–51.9%; and non-speed-sensitive executive function 5.3–57.7%. For remission BD youth patients aged ≤ 18 years, the cognitive domains impaired are verbal learning, verbal memory, working memory, visual learning, and visual memory, working memory. Attention and vigilance, reasoning and problem solving, verbal fluency, and speed of processing were not significantly impaired.²¹ More severe BD caused more cognitive impairment. The number of episodes, life stress, illness severity and progression, and long-term antipsychotic medication use affect these cognitive impairments negatively.² Cognitive impairment seems to be present from the first manic episode, although it still can be managed in the year after.²² A meta-analysis concluded that

BD patients had milder cognitive impairments, especially in attention and social cognition than schizophrenia patients.²³

These multiple domain cognitive impairments can contribute to general function impairments, which refer to physiological actions, execution of tasks, and involvement in many things including interpersonal, civic life, education, community, occupation, domestic, social, and self-care.⁴ If a person has a bad general function, it can adversely influence real-world difficulties such as psychosocial outcomes, occupational function including the capacity to perform in work of household parts and school, reduced employment, as well as their mental health and general health.^{4,20} Cognitive impairment is correlated with mood episodes. Executive function, verbal learning, verbal memory, attention, and reaction time have been associated with poorer general function in hypomania, mania, and depressed BD patients.⁴

The etiology of cognitive impairment in BD patients is not fully understood. Increasing evidence suggests that cognition may be influenced by molecular changes due to inflammation and oxidative stress, such as TNF- α (Tumor Necrosis Factor- α), CRP (C-reactive protein), interleukin-6 (IL-6); can these are influenced by bad lifestyle habits. Decreased Brain-Derived Neurotrophic Factor (BDNF) could worsen verbal fluency and executive performance. Some convinced brain structural abnormalities such as increased white matter, ventricular enlargement, and reduced anterior cingulate, prefrontal, whole brain, and insula volumes may have relationships with cognitive function.²⁴ Hypoactivity in the dorsolateral prefrontal cortex (dlPFC) and the ventrolateral prefrontal cortex is found in BD in remission when activated working memory and strategic encoding function.¹⁸

Some pharmacological and non-pharmacological treatments are promising in treating cognitive impairment in bipolar disorder. A systematic review by Tamura et al. found that lurasidone, erythropoietin, creatine monohydrate, mifepristone, *Withania somnifera*, intranasal insulin, rTMS, tDCS, and cognitive remediation seemed to give benefit in cognitive function. In contrast, no effects were found on functional remediation, psychoeducation, pramipexole, n-acetyl cysteine, and methylene blue in managing cognitive impairments in BD.²⁵

There are many ways to prevent cognitive impairment in bipolar disorder. Because some cognitive domains are associated with BD episodes, we can prevent the episodes with effective drugs and implement a psychoeducation approach. Subclinical depressive symptoms must also be handled.²² Substance use disorders, anxiety, attention deficit hyperactivity disorder are some co-occurring factors that can worsen the neurocognitive performance.²¹ Promoting a healthy lifestyle, and doing aerobic exercise to prevent overweight or obesity are also crucial.²²

The Effects of Cognitive Remediation Therapy in Bipolar Disorder Patients

We found ten articles that covered the effects of CR in BD. Nine studies are randomized-clinical trial studies, and one is a systematic review. The CR type used where group CR as has been done by Demant et al. in one RCT, computerized CR (CIRCuiTS) in three RCT, and ABCR in five RCT. The group CR and computerized CR (CIRCuiTS) were held for 12 weeks, while ABCR was held in 10 weeks. The summary of included studies can be seen in Table. 1.

The participants range from 13 to 80 participants, and most of the participants are in partial or full remission (full remission: ≤ 7 , partial remission: 8–14 on Hamilton Depression Rating 17-items Scale (HDRS) and the Young Mania Rating Scale (YRMS)). Two studies include BD with subjective cognitive impairments, assessed with Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire or PDQ (Perceived Deficits Questionnaire). Five studies include BD with objective cognitive impairments, assessed with SCIP (Screen for Cognitive Impairment in Psychiatry).

Many studies showed that CR and ABCR could improve executive functions. CR had a statistically significant effect on the executive functions at weeks 13 and 25.⁶ 10 weeks of ABCR could improve executive functions (especially planning skills)^{27,28}, and this was also associated with less pre-treatment dPFC thickness³⁰. One study found that CR gave medium-to-large effects on working memory,¹⁴ but this result contrasts with Macoveanu et al., which claimed that CR didn't alter the task-related prefrontal engagement during strategic memory encoding and working memory engagement.¹⁹ This executive function improvement did not influence by baseline subjective difficulties but had relation to pre-treatment executive dysfunction.²⁷

For the attention domain, CR could improve attention at week 13 after ABCR, and CR that involved distinct cognitive operations training resulted in medium-to-large effects on processing speed after 25 weeks.^{14,29} But another study showed that the ABCR didn't improve the speed of complex cognitive processing.²⁸ This difference may suggest that CR could give a better outcome on processing speed.

For learning and memory, CR could improve memory recall function after 25 weeks follow up.⁶ A statistically significant effect on the verbal memory was also found after 13 weeks of CR or 10 weeks of ABCR.^{28,29} However, the effect was no longer significant at the 6 months follow-up and only the subjective cognitive function persists.²⁸ CR also could improve psychosocial function by engaging in real-world activities and navigating workplace situations,¹⁴ and medium improvement were shown³¹. Unfortunately, there were no recent studies that discuss the effects of CR on language and perceptual-motor function.

Only a few studies research how CR affects brain function. Macoveanu et al. investigated the effects of an ineffective CR on dPFC (dorsal prefrontal cortex) response. The participants performed a strategic episodic picture encoding task and a spatial n-back working memory task under functional magnetic resonance imaging (fMRI). Their results was the task-related prefrontal engagement was not altered by CR.²⁶ Four years later, they changed the methods with ABCR and wanted to see if ABCR could result in neuronal changes related to memory improvement. At baseline, patients showed encoding-related hypoactivity in dPFC. Their results were ABCR improved verbal learning and memory that occurred through strategic processing, but did not change significant task-related neuronal activity.¹⁹ But these findings were contradictory with Ott et al., which found that ABCR was associated with an early dPFC activity increase.²⁹ Tsapekos et al. studied how cognitive improvements following CR translate into long-term functional improvements. After 13 weeks, participants receiving CR showed significant improvements in individual cognitive tests (including processing speed, attention and working memory, verbal memory, and executive functioning), and the global cognition composite score (average of individual domain z scores)

Table. 1 Summary of Included Studies

Reference	Type of Study	Groups	Durations	Participants	Instruments used / methods of measurement	Main results
Macoveanu et al., 2018 ²⁶	RCT	Group CR vs standard treatment	12 weeks	13 (BD patients in partial remission with subjective cognitive impairments)	Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, Encoding task, fMRI	CR didn't alter the task-related prefrontal engagement during strategic memory encoding and working memory engagement.
Bellani et al., 2019 ¹⁴	Systematic review	CR vs FR/standard treatment /CG	12-21 weeks	26-75 (BD patients)		CR that involved distinct cognitive operations training improved working memory, problem-solving, and processing speed. Specific cognitive strategies to set goals, engage in real-world activities, and navigate workplace situations improved occupational, psychosocial, and interpersonal function.
Miskowiak et al., 2021 ²⁷	RCT	ABCR standard treatment vs	10 weeks	53 (BD patients in full or partial remission with objective cognitive impairments)	SCIP, executive functions composite score, RBANS Digit Span, SWM, TMT B, verbal fluency letters "S" and "D", WAIS-III LNS	ABCR predicted greater executive functions.
Ott et al., 2021 ²⁸	RCT	ABCR standard treatment vs	10 weeks	58 (BD patients in full or partial remission with objective cognitive impairments)	SCIP, composite score, OTS, RAVLT, RBANS Coding, verbal fluency letters "D" and "S", WAIS-III LNS, RBANS Digit Span, TMT B, and TMT A, the RVP, SWM	ABCR affected executive functions, subjective cognitive functioning, verbal memory, and spatial working memory, but not the speed of complex cognitive processing. But, after 6 months, only the subjective cognition effect persists.
Strawbridge et al., 2021 ⁶	RCT	Computerized CR (CIRCuiTS) vs standard treatment	12 weeks	60 (BD patients in full remission)	DSST, SS, DS, VPA1, VPA2, current IQ, verbal fluency, Hotel test, PDQ, UPSA, FAST, GAS	CR improved functional capacity at week 13; psychosocial functioning, goal attainment, IQ, working memory, and executive function at weeks 13 and 25; global cognition, memory recall, verbal fluency, and processing speed improved at week 25.

Table. 1 Summary of Included Studies (continued)

Reference	Type of Study	Groups	Durations	Participants	Instruments used / methods of measurement	Main results
Tsapekos et al., 2021 ²⁹	RCT	Computerized CR (CIRCuiTS) vs standard treatment	12 weeks	80 (BD patients in full remission)	Wechsler Adult Intelligence Scale 4th edition, Wechsler Memory Scale 4th edition, Hotel test, FAST, GAS	CR improved individual cognitive tests, global cognition composite score, and functional outcomes at week 13. CR also improved goal attainment, verbal memory, processing speed, and working memory at week 25, but not participants with a low cognitive level at week 13.
Ott et al., 2021 ²⁹	RCT	ABCR vs standard treatment	10 weeks	45 (BD patients in full or partial remission with objective cognitive impairments)	SCIP, OTS, SWM, fMRI	ABCR was associated with an early increasing dPFC activity, so that improving working memory.
Mogensen et al., 2021 ³⁰	RCT	ABCR vs standard treatment	10 weeks	45 (full or partial remission with objective cognitive impairments)	SCIP, OTS	ABCR improved executive function. Less pre-treatment dPFC thickness was associated with greater executive function response to ABCR.
Tsapekos et al., 2022 ³¹	RCT	Computerized CR (CIRCuiTS) vs standard treatment	12 weeks	80 (BD patients in full remission with subjective cognitive impairments)	PDQ, Wechsler Adult Intelligence Scale 4th edition, VPA2, Hotel test, FAST, GAS	CR improved goal attainment, especially BD with better baseline cognitive performance, severe baseline subjective cognitive, and completed psychological therapies; global cognition, and individual cognitive domains.
Macoveanu et al., 2022 ¹⁹	RCT	ABCR vs standard treatment	10 weeks	45 (BD patients in full remission with objective cognitive impairments)	SCIP, RAVLT, RBANS Digit Span, Spatial Working Memory, TMT B, verbal fluency letters "S" and "D", WAIS-III Letter-Number Sequencing, fMRI	ABCR improved verbal learning and memory that occurred through strategic processing but did not change significant task-related neuronal activity.

ABBREVIATIONS (alphabetical order): **ABCR**: action-based cognitive remediation therapy, **BD**: bipolar disorder, **CG**: computer games, **CR**: cognitive remediation therapy, **dPFC**: dorsal prefrontal cortex, **DS**: digit span, **DSST**: digit symbol substitution test **FR**: functional remediation therapy, **fMRI**: functional magnetic resonance imaging, **GAS**: Goal Attainment

Scale, **MDD**: Major Depressive Disorder, **OTS**: One Touch Stocking of Cambridge, **PDQ**: perceived deficits questionnaire, **RAVLT**: Rey Auditory Verbal Learning Test, **RBANS**: Repeatable Battery for the Assessment of Neuropsychological Status **RCT**: randomized clinical trial, **RVP**: Rapid Visual Information Processing, **SCIP**: Screen for Cognitive Impairment in Psychiatry, **SS**: symbol search test, **SWM**: Spatial Working Memory, **TMT**: Trail Making Test, **UPSA**: UCSD performance-based skills assessment, **VPA**: verbal paired associates, **WAIS-III LNS**: Wechsler Adult Intelligence Scale Version III Letter–Number Sequencing

compared to standard treatment. This was also the case for the functional outcomes (autonomy, occupation, cognition, financial issues, interpersonal relationships, leisure time). This suggested that functional difficulties can be reduced through improvements in cognition.²⁹

Tsapekos et al. also found that CR largely improved goal attainment, especially BD with better baseline cognitive performance; severe baseline subjective cognitive, and completed psychological therapies; global cognition; and individual cognitive domains. Their other findings were medium effect size for global cognition, small-to-medium effect sizes for individual cognitive domains, and medium improvement in psychosocial functioning.³¹ These results were in line with Strawbridge et al., which state that CR largely improves goal attainment, psychosocial functioning, IQ, working memory, and executive function at both post-treatment (week 13) and follow-up (week 25). From the participant's perspective, CR itself also had good acceptability

(95%), good durations of sessions (86%), and good at increasing awareness (76%).¹⁶

The strength of this study is that we used up-to-date publications, and 90% of them are randomized-control trials. The limitations of this study are we didn't consider the variative instruments used in each paper, small sample sizes, and the characteristics of the patients were not fully uniform. Participants in partial remission were included and may affect treatment efficacy. There were still two studies using subjective cognitive impairments for inclusion criteria. Testing objective cognitive impairments is necessary to assess the cognitive function of BD.³² The pharmacological treatment, duration of illness, and the number of mood episodes were also not restricted in this study. And in some studies, therapists and participants were unblind. The duration of the intervention may also be too short. For instance, the benefit of CR in schizophrenia are found after longer-term (average 16.7 weeks) and mainly in individualized CR intervention.⁸

CONCLUSION

From the studies, we can conclude that CR has some effects in BD patients related to multiple cognitive domains (global cognition, executive function, attention, learning, and memory), IQ, psychosocial function, functional outcomes, and goal attainment. More high-quality randomized trials with objective cognitive impairments as inclusion criteria of the participants, the longer intervention of CR, better control of bias, language and perceptual-motor function observed, and the bigger sample size are required.

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