Neuropsychiatric Disease and Treatment

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Functional Remediation Improves Serum BDNF and TrkB Levels in Euthymic Patients with Bipolar Disorder: A Randomized Trial Study

Ru Li[1,*], Jiaxin Li[1,*], Shiyi Suzy Ji[2], Dazhi Li[1], Lijun Chu[1], Jian Zhang[1], Xia Sun[1], Xingguang Luo[3], Yong Zhang[1]

[1]Unit of Bipolar Disorder, Tianjin Anding Hospital, Tianjin, People's Republic of China; [2]Department of Counseling and Clinical Psychology, Teachers College, Columbia University, NY, New York, USA; [3]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

*These authors contributed equally to this work

Correspondence: Yong Zhang, Unit of Bipolar Disorder, Tianjin Anding Hospital, 13 Liulin Road, Hexi District, Tianjin, 300222, People's Republic of China, Tel/Fax +86 22 8818 8258, Email zhangyong@tjmhc.com

Purpose: We aimed to verify the impact of functional remediation (FR) on serum brain-derived neurotrophic factor (BDNF) and tyrosine kinase receptor B (TrkB) levels, to explore the biomechanism of FR intervention in patients with euthymic bipolar disorder (BD).

Patients and Methods: This is a randomized controlled, 12-week intervention study with participants randomized into the FR group (n=39) and the treatment as usual group (TAU, n=42) at the 1□1 ratio. 17-Hamilton Depression Rating Scale-17 (HDRS-17), Young Mania Rating Scale (YMRS), and Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) were used to assess affective symptoms and cognitive functioning both at baseline and week 12, respectively. Meanwhile, we collected blood samples (10 milliliters) from all participants for determination of serum BDNF/ TrkB levels both at baseline and week 12. After baseline assessment, all participants received FR or TAU treatments, respectively.

Results: Our results showed significant decreasing in HDRS-17 and YMRS scores, increasing in serum BDNF and TrkB levels in both groups over 12 weeks (all *p*'s<0.05). There were no group differences in the HDRS-17 and YMRS scores (all *p*'s>0.05), but the FR group showed greater increasing in serum BDNF and TrkB levels than those in the TAU group (all *p*'s<0.05). In terms of cognition, the change in serum BDNF levels was negatively correlated with changes in Mazes test, and the improved TrKB levels were associated with improved Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) in the FR group (all *p*'s<0.05).

Conclusion: The changes in serum BDNF and TrkB levels may be implicated in the mechanisms underlying FR intervention in euthymic patients with BD.

Limitation: A longer follow-up period than 12 weeks and set up healthy controls may make the results more convincing, and the sample size of this study is still insufficient.

Keywords: functional remediation, TAU, serum BDNF/TrkB levels, neurocognitive functioning, bipolar disorder

Introduction

Bipolar disorder (BD) is a chronic mental illness characterized by pathological and unstable mood episodes of depression and mania or hypomania, potentially leading to cognitive and psychosocial impairment, increased mortality, and reduced quality of life for patients.[1,2] Approximately 60% to 70% of patients with BD suffer from varying degrees of impairment in social and occupational functioning.[3] Cognitive deficits persist in BD patients even during periods of remission,[4] potentially hindering treatment response and functional recovery.[5] While pharmacological treatments effectively reduce clinical symptoms, there remain challenges in achieving cognitive recovery.[6]

In recent years, the field of psychological interventions has made significant achievements aimed at restoring cognitive functioning in BD. A new therapeutic intervention named Functional Remediation (FR), proposed by Martinez-

Received: 28 October 2024
Accepted: 18 January 2025
Published: 25 January 2025

Aran et al, is designed for patients with BD.[7] It belongs to a psychosocial program that offers neuropsychological training to improve cognitive deficits by incorporating exercise strategies into their daily routines.[8] Recent findings have demonstrated that FR can enhance psychosocial, occupational, and cognitive functioning, alleviate depressive symptoms, and ultimately improve the daily functioning of patients with BD,[7,9–12] with sustained effects over time.[13] However, not all patients with BD benefit from FR intervention,[14] and its mechanism still remains elusive. Therefore, the discovery of biomarkers related to cognitive impairment in psychiatric diseases has opened new avenues for exploring the mechanisms underlying FR treatment,[15] particularly for euthymic patients with BD.

BD patients present abnormal functional connectivity and structural alterations of the hippocampus, a pivotal hub of emotion regulation and cognition.[16,17] Brain-derived neurotrophic factor (BDNF), a small molecule dimer protein, promotes the growth and differentiation of neurons and highly expressed in hippocampus.[18] To date, the correlation of BDNF and treatment in BD has garnered significant attention. A finding indicated that BDNF levels decrease in euthymic patients with BD,[19] but mood stabilizers (MS) could potentially reverse BDNF levels in the hippocampus.[20,21] It is well known that BDNF plays a pivotal role in neurogenesis and cognitive functioning in euthymic patients with BD.[19,22] Mosiołek A et al pointed out that BDNF could be an indicator of cognitive function under psychotherapy in psychiatric patients.[23] However, the association between FR and the change in BDNF levels is still inconclusive. Compared to psychoeducation or pharmacological treatment, FR could effectively improve psychosocial functioning without affecting peripheral BDNF levels in euthymic BD patients.[24] In contrast, Vinogradov et al found that BDNF levels significantly increase under the treatment of cognitive remediation (CR), and serum BDNF levels could be the biomarker for the effects of CR in schizophrenia (SCZ) patient.[25] Therefore, it seems necessary to focus on changes in serum BDNF levels in euthymic BD patients under FR treatment to optimize therapies.

The role of tropomyosin-related kinase receptor type B (TrkB), belongs to the neurotrophic receptor of growth factor BDNF,[26] regulates neurotransmitter release, ion channel activity, axonal pathfinding and neuronal excitability[27] and is also unclear in the efficacy of FR treatment for BD. A previous finding has revealed that both manic and depressive-like behaviors may be associated with decreased concentrations of TrkB in BD.[28] In the mice model, therapeutic TrkB agonism and increased TrkB expression might improve cognitive function,[29] and exercise can also improve cognitive function by increasing TrkB and BDNF expression.[30] BDNF-TrkB signaling plays a key role in the development of cognitive functioning,[31] as well as TrkB neurotrophin receptors rescuing both behavioral and synaptic plasticity deficits associated with psychiatric disorders, including BD.[32] Therefore, it is meaningful to explore the potential role of TrkB levels in effects of FR treatment on cognitive functioning in euthymic BD patients.

To our knowledge, this study is the first to investigate the effects of FR on changes in serum BDNF and TrkB levels after a 12-week intervention in euthymic BD patients. Given the significant role of BDNF and TrkB in cognitive function, we hypothesize that: (i) changes in serum BDNF and TrkB levels and cognitive function are significantly higher in the FR group compared to the TAU group; (ii) changes in serum levels of BDNF and TrkB correlate with some subtypes of cognition in the FR group; (iii) serum levels of BDNF and TrkB may mediate the cognitive improvements achieved by FR intervention. We aim to verify the impact of FR on serum levels of BDNF and TrkB, and to explore the biomechanism of FR in euthymic patients with BD.

Materials and Methods

Participants

Euthymic patients with BD aged 18–60 years were consecutively recruited from Tianjin Anding Hospital between November 2019 and October 2020. All patients met the diagnosis of BD according to the Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition criteria (DSM-IV) (APA, 1994). Euthymic BD patients were defined as those with Young Mania Rating Scale (YMRS) total score ≤ 6, a 17-item Hamilton Depression Rating Scale (HDRS-17) total score ≤ 8, with clinical remission based on the criteria defined by the International Society for Bipolar Disorder (ISBD) Task Force for at least one month.[33] We excluded patients with physical diseases that could affect neuropsychological performance, such as nervous system disease (eg, epilepsy, Parkinson's disease, or multiple sclerosis), chronic infectious diseases (eg, acquired immunodeficiency syndrome), or other significant physical illnesses (eg, endocrine or metabolic

disorders), as well as any history of comorbid alcohol or drug abuse. Additionally, individuals with severe psychiatric conditions including schizophrenia (SCZ), mental retardation, and major depressive disorder were excluded. Furthermore, BD patients who had undergone other physical treatments such as modified electroconvulsive therapy (MECT) and repetitive transcranial magnetic stimulation (rTMS), as well as had received formal psychotherapy prior to enrollment were also excluded. All participants underwent inquest the case history and physical examinations, and those with abnormal results were excluded. Finally, 115 patients with BD were screened; finally, 90 patients were included for analyses. Only 25 participants were excluded due to patients with BD in depressive or manic phase and (6 patients), failure to complete the assessment (2 patients), lack of interest (3 patients), and undergo other physical treatments (14 patients).

The study protocol was approved by the Ethics Committee of Tianjin Anding Hospital (ethics committee registration number: 2019-20). Written informed consent was obtained from all participants. This study was registered on http://www.chictr.org.cn/ (Identifier number: ChiCTR1900025993), and the registration date was September 17, 2019.

Assessments and Materials

The basic demographic information of the participants, including age, gender, education levels, marital status, occupation, duration of BD, BD subtype, family history, and medications, was collected via an interview. The mood symptoms were assessed using the HDRS-17 and YMRS both at baseline and week 12 for all participants. The HDRS-17 assesses recent depressive symptoms and severity with 17 items scored between 0 and 4.[34] YMRS consists of 11 items scored from 1 to 5 points to evaluate manic symptoms and severity.[35] Higher scores indicate more severe symptoms in both the HDRS-17 and YMRS.

The neurocognitive assessment tool used The MATRICS Consensus Cognitive Battery (MCCB), which included: (1) The speed of processing: Trail Making Test-A (TMT-A) and the Brief Assessment of Cognition in Schizophrenia-Symbol Coding (BACS-SC); (2) Verbal learning and visual memory: Hopkins Verbal Learning Tests-Revised (HVLT-R), Brief Visuospatial Memory Test-Revised (BVMT-R) and Wechsler Memory Scale-III (WMS-III). (3) Verbal Fluency Test (VFC): Response fluency. (4) Reasoning and problem solving skills: Maze test. (5) Attention/ alertness: Continuous Performance Test-identical pairs version (CPT-IP). (6) social cognition: Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT). The standard T-scores were recorded for each dimension, with a lower score indicating more severe cognitive impairment. Previous findings highlight the excellent psychometric properties of the Chinese version of MCCB and demonstrate its effective application in BD.[36,37]

All assessments were conducted in quiet, private rooms with minimal distractions. Each participant was tested individually and instructed to sleep well (as much as possible) the night before assessments and to entirely avoid use of alcohol or non-prescribed drugs on the day of assessments. Cognitive tests were undertaken as close as possible to 1–4 PM to standardize daily fluctuations in alertness.[38]

Serum BDNF/TrkB Concentration Testing

We collected blood samples (10 milliliters) from euthymic BD patients to determine serum BDNF and TrkB levels both at baseline and week 12. Blood samples were collected into anticoagulant-free tubes between 7 and 8 AM and immediately transferred to the laboratory for serum preparation. The blood samples were divided into two aliquots, one for BDNF and the other for TrkB testing. To decrease possible variability, all blood samples were processed within 1 hour of being collected. After 1-hour incubation, the serum sample was separated by centrifugation and stored at −80°C for further analyses. Analyses were performed by commercial ELISA kit (Promega, USA) using a commercial kit according to the manufacturer's instructions (ChemiKine, Millipore).[39] BDNF and TrKB measurements for each participant were performed in duplicates by investigators who were blind to the state of participants. A calibrator and positive control were provided with each ELISA kit. The coefficients of inter-assay and intra-assay variations were both below 10%.

Randomization and Blinding

This is a randomly controlled, 12-week intervention study. All enrolled patients were randomly assigned to the FR group and the treatment as usual (TAU) group using a computer-generated list of random numbers by an independent statistician. This was stored on paper and kept in an opaque sealed envelope that was opened by the research coordinator at randomization to keep the allocation confidential. Furthermore, group allocation was kept confidential to patients and all researchers before enrollment. The sequence was randomly generated by the website www.sealedenvelope.com. Participants, FR trainer, and physicians were not blinded, whereas assessors and data analyst level were masked to randomization probabilities.

Procedures and Treatments

FR was developed initially by Dr. Vieta to promote cognitive impairments in patients with BD.[40] According to the FR manual program, FR consists of 21 sessions and focuses particularly on psychoeducation on cognitive deficits, improving attention, memory, executive functions, and their impacts on daily life. Attention and memory training sessions mainly need to be completed within 12 weeks, while other training sessions should be finished between 12 weeks and the endpoint.[41] The FR was conducted for 90 minutes in each session, once a week, with 6–8 participants per group. In our study, FR intervention focused on the improvement of attention, memory, and partial executive function. Given this, our study utilized a modified version of the original FR program with 12 sessions to be appropriate and relevant to all subjects to achieve targeted cognitive improvements in a shorter timeframe. These 12 training sessions consisted of the following three phases: (i) general introduction of FR, (ii) understanding cognitive impairment, (iii) cognitive training attention, memory, and partial executive functions. Each session lasted one and half hours, and the sessions were held weekly. Our previous findings have evidenced the effectiveness of this modified FR on psychosocial function in BD patients.[42] Adherence to the FR protocol was closely monitored throughout the intervention. Participants were regularly reminded about the schedule and importance of attending each session, and attendance was recorded for every session. Additionally, only one same psychiatrist responsible for the FR intervention who underwent rigorous training provided by senior psychologists and were regularly supervised throughout FR. Furthermore, the last minutes of each session are dedicated to explaining the following week's homework. Relatives are asked to encourage the patient to attend the sessions and do the homework, and to promote his or her autonomy whenever possible. Periodic checks will be conducted to ensure participants in FR group were engaging with practice. These measures adherence to the FR protocol was monitored and integrity of its delivery. The effectiveness of the programme is assessed using a comprehensive neuropsychological assessment and measures of functionality.[7]

The TAU group received 12 weeks of regular medication treatment. During this period, patients were assessed for various aspects, including the severity of clinical symptoms per session, serum BDNF/TrkB levels, and cognitive function both at baseline and endpoint. All participants were assessed by one experienced psychiatrist who was blinded to the intervention conditions. All participants received pharmacological treatment following guidelines for the management of BD, which included MS such as valproates, lithium carbonate, and lamotrigine, as well as atypical antipsychotic drugs like olanzapine, risperidone, quetiapine, and aripiprazole. Some sedative-hypnotic medications, specifically zopiclone (7.5 mg/day) and zolpidem (5–10 mg/day), were prescribed for insomnia. Intermediate- to long-acting benzodiazepines, such as clonazepam and alprazolam, were excluded due to the presence of cognitive impairment.

Statistical Analysis

Date was analyzed using SPSS version 16.0 for Windows (SPSS, Chicago, IL, USA). A chi-square test or Fisher's Exact Test, and an independent-sample *t*-test were applied to compare the demographic and clinical variables, and ratio of chosen medications between the FR group and the TAU group, respectively. Additionally, an independent samples *t*-test was conducted using baseline data to compare differences in the HDRS, YMRS scores, cognitive function, as well as serum BDNF and TrkB levels between groups. Repeated-measures analyses of variances (ANOVA) were conducted to assess the impact of the two different interventions on HDRS, YMRS scores, serum BDNF and TrkB levels, and cognitive function from baseline to the postintervention assessments. The intervention-by-time interactions were analyzed to examine the effects within and between groups. Tukey post hoc tests were performed to compare the endpoint

variables between groups. We used Mauchly's test of sphericity as a fundamental assumption for repeated measures ANOVA. If the assumption was violated, a Greenhouse–Geisser correction was applied. After controlling for age, educational level, and duration of BD, Partial correlation analysis was used to assess the correlation between changes in the serum BDNF/TrkB levels and the cognitive function in BD patients. All statistical tests were two-tailed, and the alpha was set at 0.05.

Results

Demographic Characteristics

We recruited a total of 90 euthymic BD patients for our study. Nine BD patients were excluded: four from the FR group and two from the TAU group due to unwillingness to continue the 12-week intervention and relapse, and two from the FR group and one from the TAU group due to incomplete assessments and serum sample testing. There were no differences in any variables, including baseline sociodemographic and clinical characteristics, between the excluded patients and those included (all p's > 0.05). A total of 81 participants, comprising 39 patients in the FR group and 42 patients in the TAU group, completed the final assessments, serum BDND and TrkB detection and 12-week intervention. Figure 1 illustrates the patient disposition for the present post-hoc analyses. Although variables were not considered for the randomization assignment to both groups, allocation was balanced between groups.

No significant differences were observed in age, gender, educational levels, marital status, occupation, family history, BD subtypes, and duration between the FR and TAU groups. Also, no significant differences were found in the ratio of MS and combined atypical psychotic medications between groups (p's> 0.05). See Table 1.

Comparisons of Clinical Variables Between the Groups at Baseline

We conducted independent samples t-tests to analyze baseline data on clinical variables, comparing HDRS, YMRS, serum BDNF, and TrkB levels between the FR and TAU group. There were no significant differences observed in HDRS (5.1±2.9 vs 5.4±3.5, $t = 0.01$, $p = 0.99$), YMRS (2.3±1.9 vs 2.6±2.0, $t = 1.48$, $p = 0.14$), serum BDNF levels (14.4±1.3

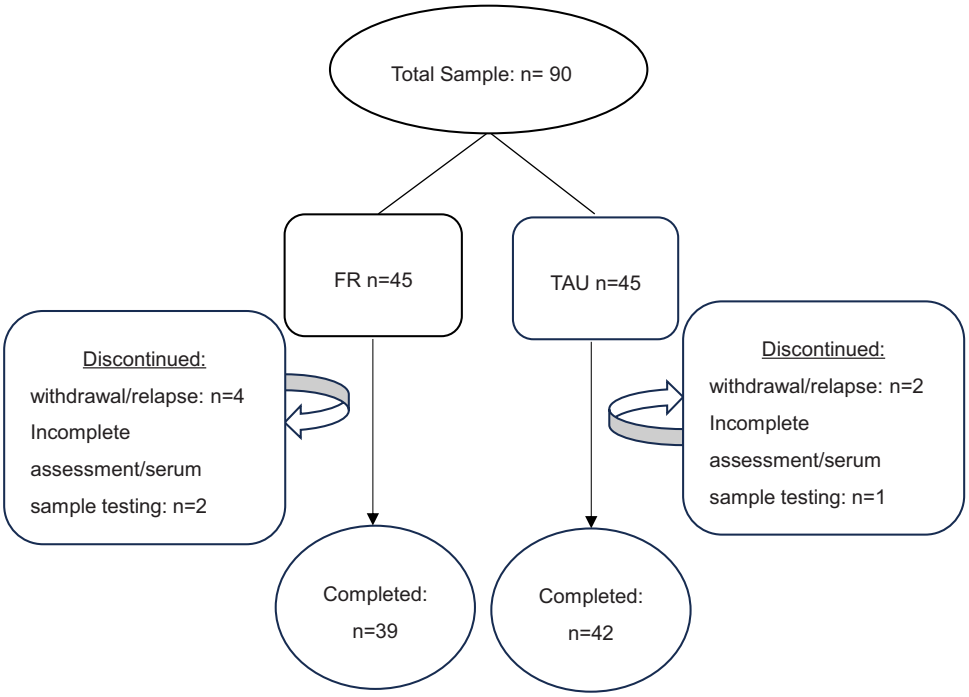

Figure 1 Flow-chart for post-hoc analyses BP patients.
Abbreviations: FR, functional remediation; TAU, treatment as usual.

https://doi.org/10.2147/NDT.S502176

Table 1 Demographic Characteristics of All Participants

Contents	FR† Group (n=39)	TAU† Group (n=42)	t/χ^2	*p* value
Age (years)*	32.3±9.3	36.5±13.8	−1.58	0.12
Sex (male/female)			0.44	0.51
—Male (n, %)	13 (33.3%)	17 (40.5%)		
—Female (n, %)	26 (66.7%)	25 (59.5%)		
Education levels (year)[a*]	14.2±2.8	13.4±2.9	1.31	0.20
Marriage (n, %)			0.27	1.00
—Married	16 (41.1%)	16 (38.1%)		
—Single	21 (53.8%)	23 (54.8%)		
—Divorce	2 (5.1%)	3 (7.1%)		
Occupation (yes/no)	26/13	30/12	0.22	0.64
Family history (no/yes)	36/3	38/4	0.09	0.77
BD subtype (I /II type)	26/13	29/13	0.05	0.82
Duration of illness (year)*	9.1±6.3	9.2±10.7	−0.05	0.96
Current duration (month)*	3.9±4.1	3.5±2.6	0.51	0.61
Mood stabilizer (n, %)			0.03	0.98
Lithium	11 (28.2%)	12 (28.6%)		
Valproate	22 (56.4%)	23 (54.8%)		
Lamotrigine	6 (15.4%)	7 (16.6%)		
Combined SGA[a†] (n, %)			0.15	1.00
Olanzapine	9 (23.1%)	10 (23.8%)		
Risperidone	12 (30.7%)	13 (31.0%)		
Quetiapine	15 (38.5%)	16 (38.1%)		
Aripiprazole	3 (7.7%)	3 (7.1%)		

Notes: *: Mean±SD; a: Fisher's Exact Test.
Abbreviations: †: FR, functional remediation; TAU, treatment as usual; SGA, atypical psychotic drug.

ng/mL vs 14.5±1.4 ng/mL, $t = -0.60$, $p = 0.55$) and TrkB levels (4.1±0.7 ng/mL vs 4.2±0.6 ng/mL, $t = -0.84$, $p = 0.41$) between the groups.

Using baseline data, we found that the FR group had higher scores on MSCEI in MCCB compared to the TAU group (44.1±3.2 vs 42.1±5.0, p=0.04). However, there were no statistically significant differences in other domains of MCCB scores between groups, including TMT-A (41.2±10.2 vs 39.9±9.8, $p = 0.58$), BACS (41.8±5.6 vs 40.5±10.4, $p = 0.50$), HVLT-R (41.2±4.2 vs 40.0±5.9, $p = 0.31$), CPT (41.7±11.1 vs 43.2±8.3, $p = 0.51$), MWS (43.3±9.1 vs 43.3±9.3, $p = 1.00$), BVMT (49.4±10.3 vs 45.4±11.9, $p = 0.11$), Fluency (45.5±10.6 vs 44.5±8.9, $p = 0.65$), and Mazes (42.7±8.3 vs 44.4±8.1, $p = 0.35$).

Clinical Variables Improvement from Pre- to Postintervention

We conducted repeated-measures analyses of variance to assess changes in clinical variables over 12 weeks. Specifically, we compared pre- and post-intervention assessments of HDRS, YMRS, MCCB, serum BDNF and TrkB levels. Our results showed significant changes in HDRS, YMRS, serum BDNF and TrkB levels over the 12 weeks in both the FR and TAU groups (all p's<0.05). When examining the interaction between the group and time (from baseline to week 12), the FR group showed greater improvement in serum BDNF ($F = 5.88$, df=1, p =0.018) and TrkB ($F = 6.47$, df=1, $p = 0.013$) levels compared to the TAU group. See Figure 2. These significant effects on serum BDNF and TrkB levels were observed after controlling for confounding variables (age and duration), while we did not observe differences in changes in HDRS and YMRS scores between the groups. Additionally, when Tukey post hoc tests were performed, the FR group did not show significantly differences in endpoint scores of HDRS, YMRS, nor in serum BDNF and TrkB levels compared to the TAU group. (all p's> 0.05).

Our results showed that all domains of MCCB, except for MWS, BVMT and MSCEIT, exhibited statistically significant differences over the 12 weeks in both FR and TAU groups (all p's < 0.05). When the interaction between

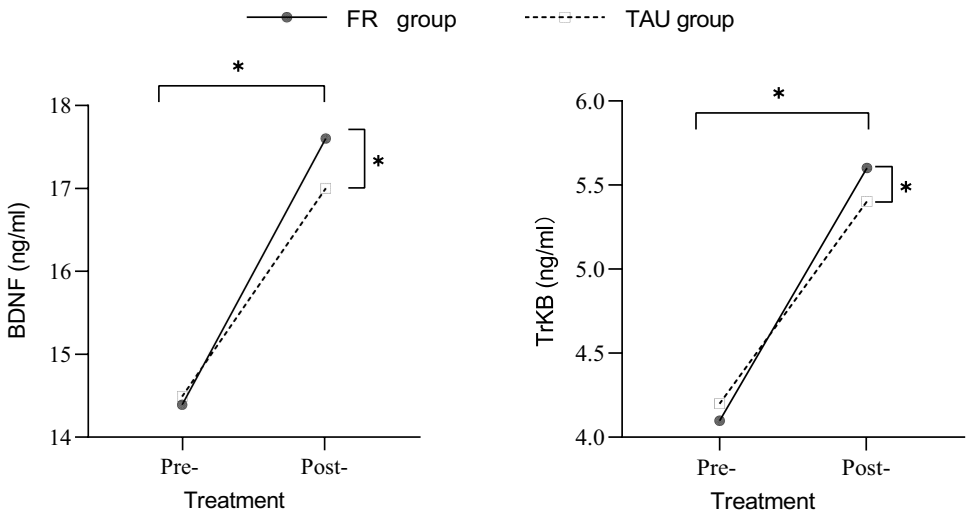

Figure 2 The comparisons of all variables between/within groups. *p<0.05.
Abbreviations; FR, Functional Remediation; BDNF, Brain-derived neurotrophic factor; TrKB, tyrosine kinase receptor B.

the group and time (from baseline to week 12) were analyzed, the FR group exhibited greater improvement in TMT-A, BACS, HVLT and CPT compared to the TAU group (all p's < 0.05). At the endpoint, the FR group showed significantly higher scores than the TAU group in TMT-A, BACS, HVLT, BVMT, and MSCEI (all p's < 0.05). See Table 2.

Associations of Cognitive Function and Serum BDNF/TrkB Levels

Using baseline data, Pearson correlation analysis showed no correlation between serum BDNF/TrKB levels and age, educational years, duration of BD, and all domains of MCCB (all p's> 0.05) among all patients with BD. After controlling for age, educational level, and duration of BD, partial correlation analysis yielded that changes in serum

Table 2 The Comparisons of All Variables Between/Within Groups

	FR† Group (n=39)		TAU† Group (n=42)		*F1*† (Within Group)	*F2*† (prepost*group)	*F3*† (Between Group)
	Pre-	**Post-**	**Pre-**	**Post-**	(*p* value)	(*p* value)	(*p* value)
HDRS†*	5.1±2.9	4.1±2.1	5.4±3.5	4.0±2.0	8.62 (0.004)	0.17 (0.684)	0.07 (0.793)
YMRS†*	2.3±1.9	1.8±1.4	2.6±2.0	1.9±1.5	5.31 (0.024)	0.06 (0.807)	0.50 (0.480)
BDNF†* (ng/mL)	14.4±1.3	17.6±1.3	14.5±1.4	17.0±1.5	298.51 (<0.001)	5.88 (0.018)	0.71 (0.403)
TrkB†* (ng/mL) †	4.1±0.7	5.6±0.5	4.2±0.6	5.4±0.5	306.92 (<0.001)	6.47 (0.013)	0.47 (0.495)
MCCB†*							
TMT-A†*	41.2±10.2	50.4±6.0	39.9±9.8	44.2±3.6	40.21 (<0.01)	5.35 (0.02)	7.04 (0.01)
BACS†*	41.8±5.6	52.5±7.4	40.5±10.4	46.2±4.2	51.62 (<0.01)	4.94 (0.03)	10.95 (<0.01)
HVLT†*	41.2±4.2	51.7±4.2	40.0±5.9	46.0±3.2	11.40 (<0.01)	8.77 (<0.01)	30.03 (<0.01)
CPT†*	41.7±11.1	51.4±5.8	43.2±8.3	45.7±2.5	30.84 (<0.01)	10.56 (<0.01)	2.76 (0.10)
MWS†*	43.3±9.1	45.2±2.7	43.3±9.3	44.6±2.6	2.54 (0.12)	0.09 (0.77)	0.09 (0.76)
BVMT†*	49.4±10.3	50.6±2.6	45.4±11.9	48.4±3.1	3.44 (0.07)	0.64 (0.43)	4.89 (0.03)
Fluency*	45.5±10.6	48.4±3.6	44.5±8.9	46.4±2.4	4.35 (0.04)	0.22 (0.64)	1.82 (0.18)
Mazes*	42.7±8.3	44.9±2.0	44.4±8.1	46.0±3.7	4.45 (0.04)	0.13 (0.72)	1.79 (0.19)
MSCEI†	44.1±3.2	44.8±3.4	42.1±5.0	42.5±2.5	0.94 (0.34)	0.10 (0.76)	12.60 (<0.01)

Note: *: Mean±SD.
Abbreviations: †: FR, functional remediation; TAU, treatment as usual; F1 represents differences of change within the group, F2 represents interaction of prepost*group (pre: before intervention, post: after intervention), F3 (posthoc tests) represents endpoint differences between the two groups, YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B; MCCB, The MATRICS Consensus Cognitive Battery; TMT-A, Trail Making Test-A; BACS-SC, the Brief Assessment of Cognition in Schizophrenia-Symbol Coding; HVLT-R, Hopkins Verbal Learning Tests-Revised, BVMT-R, Brief Visuospatial Memory Test-Revised; WMS- III, Wechsler Memory Scale-III. VFC, Verbal Fluency Test; CPT-IP, Continuous Performance Test-identical pairs version; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test.

https://doi.org/10.2147/NDT.S502176

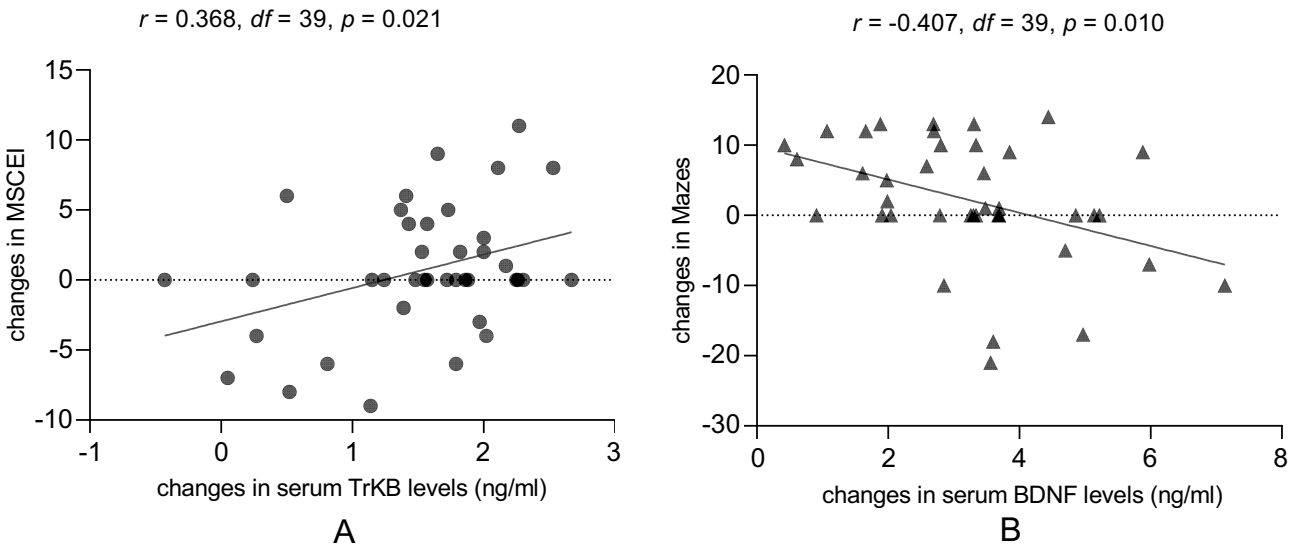

Figure 3 Associations between changes in MCCB domains and changes in serum levels of BDNF/TrKB in FR group.
Abbreviations: BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test.

BDNF levels were significantly associated with changes in Mazes (r = −0.407, df = 39, p = 0.010). See Figure 3A. Additionally, there was a positive association between changes in MSCEI and changes in serum TrKB levels (r = 0.368, df = 39, p = 0.021) in the FR group. See Figure 3B.

Discussion

This randomly controlled, 12-week intervention study aimed to examine the impact of FR on changes in serum BDNF and TrkB levels and cognitive measures among euthymic patients with BD. We compared the differences in serum BDNF, TrkB levels, cognitive function, and emotional symptoms between FR and TAU group over time. Our findings revealed that both the FR and TAU groups significantly decreased scores on HDRS-17, YMRS, but also increased serum BDNF and TrkB levels over 12 weeks intervention. Furthermore, the FR group showed significantly greater improvements in cognitive function (TMT-A, BACS, HVLT, and CPT), as well as serum BDNF and TrkB levels compared to the TAU group. While post-treatment scores for TMT-A, BACS, HVLT, BVMT, and MSCEI in the FR group were significantly higher compared to those in the TAU group, but no differences were found in endpoint HDRS-17, YMRS, serum BDNF, and TrkB levels. It was very noteworthy that changes in serum BDNF levels were negatively associated with Mazes, whereas changes in TrKB levels were positively associated with MSCEI under FR intervention. Our results are largely consistent with our study hypothesis, especially highlighting the potential link between improved levels of BDNF and cognitive functioning.

We randomly assigned all participants to the FR group and the TAU group based on a computer-generated list of random numbers, ensuring the balance for demographic and clinical variables, and medication conditions between the groups, but due to randomness, there may still be some differences in certain characteristics. Thus, no baseline group differences were found between groups in HDRS-17, YMRS, serum BDNF and TrkB level, and all dimensions in MCCB except for MSCEI. Although participants were assigned randomly to control distribution of the medication treatments to minimize bias, the possible effect of MS and antipsychotics on cognitive performance and BDNF/TrKB levels should be considered. A finding showed that psychotropic medications could worsen cognitive performance, such as attention and memory ability.[43] In addition, treatment with lithium or valproate can increase BDNF levels in euthymic BD patients.[44] Antipsychotics could have had varying effects on the BDNF levels in patients with SCZ.[45] Given BDNF and TrKB has been associated with cognition functioning in BD,[23,29] more convincing results involved patients only treated with FR but no medication. But our results have reliability as well. Furthermore, our findings demonstrated that both the FR and the TAU intervention could sequentially decrease HDRS-17 and YMRS scores in euthymic BD patients within 12 weeks,

indicating both FR and TAU intervention can alleviate depressive and manic emotions. However, no significant difference in changes of depressive and manic symptoms was detected between groups, suggesting that the FR intervention had a limited effect on sustained improvement of emotional symptoms during euthymic period. Akin to prior findings, Bonnin et al found no greater improvement in depressive and manic symptoms following a 6-month FR treatment phase compared to psychoeducation and TAU in euthymic BP patients.[24] This may be attributed to two factors: firstly, BD patients in euthymic state remained clinically stable, making it unlikely to show significant improvement in emotional symptoms; and secondly, FR was not specifically developed to relieve emotional symptoms but rather to improve neurocognitive deficits and daily functioning.[7]

In patients with BD in the euthymic phase, the cognitive domains most affected are memory, attention, and executive function.[46] A review indicated that certain interventions, such as lurasidone, lamotrigine, and CR, can effectively enhance functioning.[47] Our findings revealed that both FR and conventional medication treatments could improve cognitive impairment, specifically in speed of processing, verbal learning, visual memory, and social cognition. FR is effective at improving verbal memory in a sample of neurocognitively impaired patients with BD at a 6-month follow-up.[48] Furthermore, improvements in attention, working memory, and speed of processing were sustained even after a 1-year follow-up in patients with BD receiving FR interventions.[13] A study involving 72 patients with BD found improvements in cognitive performance, including processing speed, visual learning and memory domains, as well as the composite score, following a 70-hour computerized CR program, and efficacy maintained over 6 months post-intervention.[49] Our results were similar to previous studies, we found that scores on TMT-A, BACS, HVLT, BVMT, and MSCEI were significantly higher in the FR group compared to the TAU group after the 12-week treatment. This demonstrates that FR could effectively enhance cognitive functioning in euthymic patients with BD. Furthermore, the improvements in TMT-A, BACS, HVLT, and CPT scores were significantly greater in the FR group than the TAU group after 12-week treatment, supporting the notion that FR plays a crucial role in enhancing speed of processing, visual memory, and attention/alertness in euthymic BD patients. But Torrent et al noted that while the FR group did not show significant effects on neurocognitive variables, it effectively improved psychosocial functioning in euthymic BD patients compared to the TAU group.[50] Additionally, Demant et al found no improvement in overall cognitive following a 12-week CR intervention.[51] These inconsistent outcomes may stem from variations in neuropsychological assessment tools, illness duration, and intervention protocols. Therefore, fine-grained studies are needed to confirm these findings in patients with BD.

To date, the association between BD and BDNF remains inconsistent and even contradictory.[20,52] A recent meta-analysis revealed that peripheral BDNF levels decrease during manic and depressive episodes but do not significantly change during euthymic periods in patients with BD,[53] but BDNF levels decrease in euthymic patients with BD in another study.[19] Although our study did not directly compare serum BDNF levels between patients with BD and healthy controls (HCs), we found that both pharmacological and FR treatments led to an increase in BDNF levels. This suggests that BDNF plays a crucial role in the treatment of BD patients. In addition, our findings revealed that FR group obviously enhanced peripheral concentrations of BDNF compared to TAU group. Data from previous studies suggest an association between BDNF and cognitive function. For example, increasing serum BDNF levels may be a crucial factor in alleviating cognitive impairment.[22,54] Additionally, BDNF can serve as a biomarker for cognitive recovery in patients with SCZ.[55] Vinogradov et al identified BDNF levels as biomarkers for the effects of CR on cognitive enhancement.[25] Another finding evidenced that aerobic exercise can induce a state of neuroplastic readiness in the brain by upregulating BDNF, thereby enhancing the effectiveness of CR in patients with SCZ.[56] Based on our results, it is reasonable to infer that FR is likely to enhance cognitive performance through the increasement of serum BDNF levels. Additionally, our findings provide further evidence for the efficacy of FR as a valuable treatment in euthymic patients with BD. Another related study demonstrated that both FR and TAU improved depressive and manic symptoms without a significant increase in BDNF levels.[24] These inconsistent outcomes could be attributed to differences in recruited subjects, mediation, duration of BD, psychological interventions, and other factors. Further research is needed to explore the underlying confounding factors involved in the relationship between FR interventions and changes in BDNF concentrations.

A previous study showed that serum TrkB levels were lower in BD patient than in HCs,[57] and these levels might be associated with manic and depressive-like behaviors in BD.[28] The serum TrkB levels may distinguish BD from panic

disorder (PD) and SCZ,[57] suggesting that TrkB is a key biomarker in BD. However, to our knowledge, no studies have yet focused on changes in TrkB levels following FR intervention in patients with BD. In this study, serum TrkB levels increased after treatment in both groups, consistent with our hypothesis. Moreover, TrkB concentrations were significantly higher in the FR group compared to the TAU group, indicating that elevated TrkB levels may be involved in the cognitive improvement following FR treatment.

Furthermore, we also found that TrKB levels did not exhibit significant correlation with the impairment of cognitive function in all participants, while changes in MSCEI positively correlates with changes of serum TrKB levels in FR group, indicating that improvement in social cognition is associated with the increase in TrKB levels. A mice model suggested that upregulation of TrkB expression might improve cognitive function.[29] Acute microinjections of TrkB agonists into the medial prefrontal cortex and chronic antidepressant treatment ameliorated the social behavior and cognition.[58] Kim et al also found that the increased expression of TrkB was associated with improved cognitive function by regular exercise.[30] Another finding demonstrated that BDNF and TrkB transcripts decreased in the hippocampus and striatum in BD patients, respectively,[59] and BDNF-TrkB signaling has been shown to ameliorate cognitive deficits,[60] highlighting the critical role of BDNF and TrkB in cognitive performance. Therefore, our findings support that FR could reverse serum TrkB levels and thereby contribute to enhancing cognitive functioning. While pharmacological intervention showed limited improvement in BDNF and TrkB concentrations, consistent with a previous finding, which displayed that pharmacological treatment is less likely to restore cognitive impairment in patients with BD.[6]

Our results did not find a meaningful association between serum BDNF levels and each dimension of cognitive function. Similarly, another study concluded that there was no correlation between plasma BDNF levels and deficits in neurocognitive function in euthymic BD patients.[61] But a previous study indicated that serum BDNF levels were correlated with executive functioning, verbal memory and verbal fluency in patients with BD.[22] A study on 12-week pharmacological treatment in patients with BD showed a significant positive correlation between changes in plasma BDNF levels and improvements in executive function.[62] Sun et al pointed out a significantly positive association between the increase of serum BDNF levels and memory and attention improvement after treatment in patients with SCZ.[55,63] A review[64] pointed out that CR could reverse deficits of frontal cortex, thalamus, hippocampus, and amygdala, which are crucial to enhance problem-solving performances. We inferred that changed BDNF levels may benefit to problem-solving ability based on FR intervention. However, our finding showed that changes in serum BDNF levels were significantly negative associated with changes in Mazes. The inconsistent results may be related to differences in assessment tools, the duration of BD and interventions. In addition, rats exposed to maternal deprivation in early childhood showed functional deficits in memory and cognitive flexibility, as well as reduced BDNF expression in the hippocampus. After environmental enrichment intervention, rats were able to protect their memory and cognitive flexibility, and hippocampal BDNF expression levels were restored to normal levels.[65] Increased hippocampal volume translates to improved memory function and higher serum BDNF.[66] Therefore, we speculate that FR can increase BDNF levels in hippocampus to improve cognition functioning, which can provide a new insight into the mechanism of FR intervention. In addition, the improving effect of MS on cognitive function in patients with BD is an unavoidable confounding factor. Future studies need to control for confounding factors to verify these findings.

However, this study has some limitations. First, although the distribution of the medication treatments was controlled for between the groups using randomized method, the possible effect of MS and antipsychotics on intervention outcomes remained unavoidable. For example, different antipsychotics and lithium could have had varying effects on the BDNF levels.[45,67] Second, the 12-week observation period may not fully elucidate the long-term effects of the FR intervention on clinical symptoms, BDNF and TrkB levels. For instance, a 6-month study consisting of 21 weekly sessions reported no significant increase in BDNF levels underlying the treatment of FR compared to the TAU group,[24] Additionally, shorter intervention period may weaken the correlates between changed BDNF levels and other cognitive domains. Therefore, future studies should consider longer-term effect under FR intervention. Third, we did not establish healthy controls to demonstrate changes in serum BDNF and TrKB levels in our study, which distinguishing between normal variations and changes specifically related to serum BDNF and TrKB levels becomes challenging. For future research, it is crucial to include a control group to enhance the reliability and interpretability of results, providing a clearer understanding of the impact of variables. Fourth, testing serum BDNF/TrKB levels at baseline and week 12 may not

capture more granular changes over time to better understand the dynamics of BDNF/TrKB fluctuations. Further study should take it into account based on whole 21-weeks intervention. Last but not least, the sample size in our study was insufficient to examine the generalizability and may have weakened the statistic power when analyzing the biomechanisms of FR treatment in BD. As such, future studies with larger samples are warranted.

Conclusion

This study mainly examined the impact of FR on improving serum BDNF and TrkB levels among euthymic patients with BD. Our findings indicate that the FR significantly improved serum BDNF and TrkB levels, but did not affect affective symptoms over time. Therefore, a potential biological mechanism of FR intervention may involve the improvement of serum BDNF and TrkB levels, providing new perspectives for improving cognition functioning in euthymic patients with BD and a promising treatment strategy. Future research should focus on refining the FR therapeutic protocols and optimal treatment duration, exploring the role FR may play over the long term in cognition functioning without the intervention effects of medication treatment, and accumulating good-quality evidence to inform clinical practice.

Data Sharing Statement

The data that support the findings of this study are available from Tianjin Anding Hospital but restrictions apply to the availability of those data, which were used under license for the current study, and so are not publicly available. Data about documents of participants should be accessible and be communicated with our corresponding author according to the requirement of the Ethics Committee in Tianjin Anding Hospital.

Ethical Approval

The study protocol was approved by the Ethics Committee of Tianjin Anding Hospital (the ethics committee registration number: 2019-20) in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Acknowledgments

We express our gratitude to all participants who took part in the assessments and interviews conducted during our research. We would also like to extend our thanks to the dedicated social workers and nurses who provided invaluable assistance throughout the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Tianjin Key Medical Discipline (Specialty) Construction Project (grant numbers: TJYXZDXK-033A).

Disclosure

The authors declare that they have no conflict of interest.

References

1. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. *Nat Rev Dis Primers*. 2018;4:18008. doi:10.1038/nrdp.2018.8
2. Carvalho AF, Firth J, Vieta E. Bipolar disorder. *N Engl J Med*. 2020;383(1):58–66. doi:10.1056/NEJMra1906193
3. Henry C, Etain B, Godin O, et al. Bipolar patients referred to specialized services of care: not resistant but impaired by sub-syndromal symptoms. Results from the FACE-BD cohort. *Aust N Z J Psychiatry*. 2015;49(10):898–905. doi:10.1177/0004867415585582
4. Lima IMM, Peckham AD, Johnson SL. Cognitive deficits in bipolar disorders: implications for emotion. *Clin Psychol Rev*. 2018;59:126–136. doi:10.1016/j.cpr.2017.11.006
5. Miskowiak KW, Seeberg I, Jensen MB, et al. 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 Disord*. 2022;24(4):354–374. doi:10.1111/bdi.13193
6. Bourne C, Aydemir Ö, Balanzá-Martínez V, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand*. 2013;128(3):149–162. doi:10.1111/acps.12133
7. Solé B, Bonnin C, Mayoral M, et al. Functional remediation for patients with bipolar II disorder: improvement of functioning and subsyndromal symptoms. *Eur Neuropsychopharmacol*. 2015;25(2):257–264. doi:10.1016/j.euroneuro.2014.05.010
8. Medalia A, Freilich B. The Neuropsychological Educational Approach to Cognitive Remediation (NEAR) model: practice principles and outcome studies. *Am J Psychiatr Rehabil*. 2008;11:123–143. doi:10.1080/15487760801963660
9. Sanchez-Moreno J, Bonnín C, González-Pinto A, et al. Do patients with bipolar disorder and subsyndromal symptoms benefit from functional remediation? A 12-month follow-up study. *Eur Neuropsychopharmacol*. 2017;27(4):350–359. doi:10.1016/j.euroneuro.2017.01.010
10. Bellani M, Biagianti B, Zovetti N, et al. 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. *J Affect Disord*. 2019;257:691–697. doi:10.1016/j.jad.2019.07.059
11. Koene J, Zyto S, van der Stel J, et al. The relations between executive functions and occupational functioning in individuals with bipolar disorder: a scoping review. *Int J Bipolar Disord*. 2022;10(1):8. doi:10.1186/s40345-022-00255-7
12. Accardo V, Barlati S, Ceraso A, Nibbio G, Vieta E, Vita A. Efficacy of functional remediation on cognitive and psychosocial functioning in patients with bipolar disorder: study protocol for a randomized controlled study. *Brain Sci*. 2023;13(5):708. doi:10.3390/brainsci13050708
13. Bonnin CM, Torrent C, Arango C, et al. Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. *Br J Psychiatry*. 2016;208(1):87–93. doi:10.1192/bjp.bp.114.162123
14. Solé B, Bonnín CM, Radua J, et al. Long-term outcome predictors after functional remediation in patients with bipolar disorder - CORRIGENDUM. *Psychol Med*. 2023;53(12):5886. doi:10.1017/S0033291723001538
15. Wang Y, Meng W, Liu Z, An Q, Hu X. Cognitive impairment in psychiatric diseases: biomarkers of diagnosis, treatment, and prevention. *Front Cell Neurosci*. 2022;16:1046692. doi:10.3389/fncel.2022.1046692
16. Saccaro LF, Delavari F, Van De Ville D, Piguet C. Hippocampal temporal dynamics and spatial heterogeneity unveil vulnerability markers in the offspring of bipolar patients. *Bipolar Disord*. 2024. doi:10.1111/bdi.13487
17. Jawad MY, Qasim S, Ni M, et al. The role of ketamine in the treatment of bipolar depression: a scoping review. *Brain Sci*. 2023;13(6):909. doi:10.3390/brainsci13060909
18. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *mol Psychiatry*. 2005;10(1):105–116. doi:10.1038/sj.mp.4001585
19. Yoldi-Negrete M, Palacios-Cruz L, Tirado-Durán E, et al. Looking for factors affecting functioning in euthymic patients with bipolar I disorder: the importance of cognitive complaints and BDNF's Val66Met polymorphism. *J Affect Disord*. 2022;302:131–138. doi:10.1016/j.jad.2022.01.006
20. Chen SL, Lee SY, Chang YH, et al. Therapeutic effects of add-on low-dose dextromethorphan plus valproic acid in bipolar disorder. *Eur Neuropsychopharmacol*. 2014;24(11):1753–1759. doi:10.1016/j.euroneuro.2014.09.001
21. Jornada LK, Moretti M, Valvassori SS, et al. Effects of mood stabilizers on hippocampus and amygdala BDNF levels in an animal model of mania induced by ouabain. *J Psychiatr Res*. 2010;44(8):506–510. doi:10.1016/j.jpsychires.2009.11.002
22. Mora E, Portella MJ, Piñol-Ripoll G, et al. High BDNF serum levels are associated to good cognitive functioning in bipolar disorder. *Eur Psychiatry*. 2019;60:97–107. doi:10.1016/j.eurpsy.2019.02.006
23. Mosiołek A, Pietrzak M, Tabisz M, et al. Brain-Derived Neurotrophic Factor (BDNF) as an Indicator for Effects of Cognitive Behavioral Therapy (CBT): a systematic review. *Biomedicines*. 2022;11(1):27. doi:10.3390/biomedicines11010027
24. Bonnin CDM, Valls E, Rosa AR, et al. Functional remediation improves bipolar disorder functioning with no effects on brain-derived neurotrophic factor levels. *Eur Neuropsychopharmacol*. 2019;29(6):701–710. doi:10.1016/j.euroneuro.2019.04.002
25. Vinogradov S, Fisher M, Holland C, Shelly W, Wolkowitz O, Mellon SH. Is serum brain-derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia? *Biol Psychiatry*. 2009;66(6):549–553. doi:10.1016/j.biopsych.2009.02.017
26. Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. *J Psychiatr Res*. 2007;41(12):979–990. doi:10.1016/j.jpsychires.2006.09.009
27. Schinder AF, Poo M. The neurotrophin hypothesis for synaptic plasticity. *Trends Neurosci*. 2000;23(12):639–645. doi:10.1016/S0166-2236(00)01672-6
28. Valvassori SS, Dal-Pont GC, Varela RB, et al. Ouabain induces memory impairment and alter the BDNF signaling pathway in an animal model of bipolar disorder: cognitive and neurochemical alterations in BD model. *J Affect Disord*. 2021;282:1195–1202. doi:10.1016/j.jad.2020.12.190
29. Geraghty AC, Gibson EM, Ghanem RA, et al. Loss of adaptive myelination contributes to methotrexate chemotherapy-related cognitive impairment. *Neuron*. 2019;103(2):250–265.e258. doi:10.1016/j.neuron.2019.04.032
30. Kim TW, Choi HH, Chung YR. Treadmill exercise alleviates impairment of cognitive function by enhancing hippocampal neuroplasticity in the high-fat diet-induced obese mice. *J Exerc Rehabil*. 2016;12(3):156–162. doi:10.12965/jer.1632644.322
31. Saral S, Topçu A, Alkanat M, et al. Agomelatine attenuates cisplatin-induced cognitive impairment via modulation of BDNF/TrkB signaling in rat hippocampus. *J Chem Neuroanat*. 2023;130:102269. doi:10.1016/j.jchemneu.2023.102269

32. Tigaret CM, Lin TE, Morrell ER, et al. Neurotrophin receptor activation rescues cognitive and synaptic abnormalities caused by hemizygosity of the psychiatric risk gene Cacna1c. *mol Psychiatry*. 2021;26(6):1748–1760. doi:10.1038/s41380-020-01001-0
33. Mauricio T, Ellen F, Charles LB, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord*. 2009;11(5).
34. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278–296. doi:10.1111/j.2044-8260.1967.tb00530.x
35. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429–435. doi:10.1192/bjp.133.5.429
36. Shi C, Kang L, Yao S, et al. The MATRICS Consensus Cognitive Battery (MCCB): co-norming and standardization in China. *Schizophr Res*. 2015;169(1–3):109–115. doi:10.1016/j.schres.2015.09.003
37. Bo Q, Mao Z, Li X, Wang Z, Wang C, Ma X. Use of the MATRICS consensus cognitive battery (MCCB) to evaluate cognitive deficits in bipolar disorder: a systematic review and meta-analysis. *PLoS One*. 2017;12(4):e0176212. doi:10.1371/journal.pone.0176212
38. Strawbridge R, Tsapekos D, Hodsoll J, et al. Cognitive remediation therapy for patients with bipolar disorder: a randomised proof-of-concept trial. *Bipolar Disord*. 2021;23(2):196–208. doi:10.1111/bdi.12968
39. Zeliha T, Aysegul O, Deniz C, et al. Alterations in BDNF (brain derived neurotrophic factor) and GDNF (glial cell line-derived neurotrophic factor) serum levels in bipolar disorder: the role of lithium. *J Affect Disord*. 2014;166.
40. Bonnin CM, Torrent C, Vieta E, Martínez-Arán A. Restoring functioning in bipolar disorder: functional remediation. *Harv Rev Psychiatry*. 2014;22(6):326–330. doi:10.1097/HRP.0000000000000062
41. Vieta E, Torrent C, Martínez-Arán A. *Functional Remediation for Bipolar Disorder*. Cambridge: Cambridge University Press; 2014.
42. Zhang Y, Wang W, Xi Y, et al. Functional remediation for euthymic patients with bipolar disorder. *Chin J Psychiatry*. 2020;06:486–492.
43. Pompili M, Innamorati M, Gonda X, et al. Pharmacotherapy in bipolar disorders during hospitalization and at discharge predicts clinical and psychosocial functioning at follow-up. *Hum Psychopharmacol*. 2014;29(6):578–588. doi:10.1002/hup.2445
44. Lima Giacobbo B, Doorduin J, Klein HC, Dierckx R, Bromberg E, de Vries EFJ. Brain-derived neurotrophic factor in brain disorders: focus on neuroinflammation. *mol Neurobiol*. 2019;56(5):3295–3312. doi:10.1007/s12035-018-1283-6
45. Pandya CD, Kutiyanawalla A, Pillai A. BDNF-TrkB signaling and neuroprotection in schizophrenia. *Asian J Psychiatr*. 2013;6(1):22–28. doi:10.1016/j.ajp.2012.08.010
46. Baena-Oquendo S, García Valencia J, Vargas C, López-Jaramillo C. Neuropsychological aspects of bipolar disorder. *Rev Colomb Psiquiatr*. 2022;51(3):218–226. doi:10.1016/j.rcp.2020.08.003
47. Bonnín CDM, Reinares M, Martínez-Arán A, et al. Improving functioning, quality of life, and well-being in patients with bipolar disorder. *Int J Neuropsychopharmacol*. 2019;22(8):467–477. doi:10.1093/ijnp/pyz018
48. Bonnin CM, Reinares M, Martínez-Arán A, et al. Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory. *Psychol Med*. 2016;46(2):291–301. doi:10.1017/S0033291715001713
49. Lewandowski KE, Sperry SH, Cohen BM, et al. Treatment to Enhance Cognition in Bipolar Disorder (TREC-BD): efficacy of a randomized controlled trial of cognitive remediation versus active control. *J Clin Psychiatry*. 2017;78(9):e1242–e1249. doi:10.4088/JCP.17m11476
50. Torrent C, Bonnin Cdel M, Martínez-Arán A, et al. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *Am J Psychiatry*. 2013;170(8):852–859. doi:10.1176/appi.ajp.2012.12070971
51. Demant KM, Vinberg M, Kessing LV, Miskowiak KW. 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*. 2015;10(6):e0127955. doi:10.1371/journal.pone.0127955
52. Karthikeyan S, Dimick MK, Fiksenbaum L, et al. Inflammatory markers, brain-derived neurotrophic factor, and the symptomatic course of adolescent bipolar disorder: a prospective repeated-measures study. *Brain Behav Immun*. 2022;100:278–286. doi:10.1016/j.bbi.2021.11.020
53. Rowland T, Perry BI, Upthegrove R, et al. Neurotrophins, cytokines, oxidative stress mediators and mood state in bipolar disorder: systematic review and meta-analyses. *Br J Psychiatry*. 2018;213(3):514–525. doi:10.1192/bjp.2018.144
54. Lin CC, Huang TL. Brain-derived neurotrophic factor and mental disorders. *Biomed J*. 2020;43(2):134–142. doi:10.1016/j.bj.2020.01.001
55. Zhang Y, Fang X, Fan W, et al. Brain-derived neurotrophic factor as a biomarker for cognitive recovery in acute schizophrenia: 12-week results from a prospective longitudinal study. *Psychopharmacology*. 2018;235(4):1191–1198. doi:10.1007/s00213-018-4835-6
56. Campos C, Rocha NBF, Lattari E, Nardi AE, Machado S. Exercise induced neuroplasticity to enhance therapeutic outcomes of cognitive remediation in schizophrenia: analyzing the role of brai nderived neurotrophic factor. *CNS Neurol Disord Drug Targets*. 2017;16(6):638–651. doi:10.2174/1871527315666161223142918
57. Chen S, Jiang H, Liu Y, et al. Combined serum levels of multiple proteins in tPA-BDNF pathway may aid the diagnosis of five mental disorders. *Sci Rep*. 2017;7(1):6871. doi:10.1038/s41598-017-06832-6
58. Fernández-García S, Sancho-Balsells A, Longueville S, et al. Astrocytic BDNF and TrkB regulate severity and neuronal activity in mouse models of temporal lobe epilepsy. *Cell Death Dis*. 2020;11(6):411. doi:10.1038/s41419-020-2615-9
59. Reinhart V, Bove SE, Volfson D, Lewis DA, Kleiman RJ, Lanz TA. Evaluation of TrkB and BDNF transcripts in prefrontal cortex, hippocampus, and striatum from subjects with schizophrenia, bipolar disorder, and major depressive disorder. *Neurobiol Dis*. 2015;77:220–227. doi:10.1016/j.nbd.2015.03.011
60. Kartalou GI, Salgueiro-Pereira AR, Endres T, et al. Anti-inflammatory treatment with FTY720 starting after onset of symptoms reverses synaptic deficits in an AD mouse model. *Int J mol Sci*. 2020;21(23):8957. doi:10.3390/ijms21238957
61. Chou YH, Wang SJ, Lirng JF, et al. Impaired cognition in bipolar I disorder: the roles of the serotonin transporter and brain-derived neurotrophic factor. *J Affect Disord*. 2012;143(1–3):131–137. doi:10.1016/j.jad.2012.05.043
62. Lee SY, Wang TY, Chen SL, et al. The correlation between plasma brain-derived neurotrophic factor and cognitive function in bipolar disorder is modulated by the BDNF Val66Met polymorphism. *Sci Rep*. 2016;6:37950. doi:10.1038/srep37950
63. Sun ZL, Liu J, Guo W, et al. Serum brain-derived neurotrophic factor levels associate with cognitive improvement in patients with schizophrenia treated with electroacupuncture. *Psychiatry Res*. 2016;244:370–375. doi:10.1016/j.psychres.2016.07.040
64. Bellani M, Ricciardi C, Rossetti MG, Zovetti N, Perlini C, Brambilla P. Cognitive remediation in schizophrenia: the earlier the better? *Epidemiol Psychiatr Sci*. 2019;29:e57. doi:10.1017/S2045796019000532

65. Menezes J, Souto Das Neves BH, Gonçalves R, Benetti F, Mello-Carpes PB. Maternal deprivation impairs memory and cognitive flexibility, effect that is avoided by environmental enrichment. *Behav Brain Res*. 2020;381:112468. doi:10.1016/j.bbr.2020.112468
66. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108(7):3017–3022. doi:10.1073/pnas.1015950108
67. De-Paula VJ, Gattaz WF, Forlenza OV. Long-term lithium treatment increases intracellular and extracellular brain-derived neurotrophic factor (BDNF) in cortical and hippocampal neurons at subtherapeutic concentrations. *Bipolar Disord*. 2016;18(8):692–695. doi:10.1111/bdi.12449