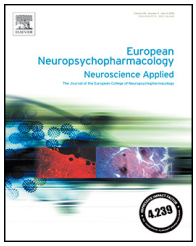
European Neuropsychopharmacology (2019) 29, 701–710

www.elsevier.com/locate/euroneuro



Functional remediation improves bipolar disorder functioning with no effects on brain-derived neurotrophic factor levels

Caterina del Mar Bonnin[a,1,*], Elia Valls[a,1,*], Adriane R. Rosa[b], Maria Reinares[a], Esther Jimenez[a], Brisa Solé[a], Laura Montejo[a], Ana Meseguer[c], Isabella Pacchiarotti[a], Francesc Colom[d], Anabel Martinez-Aran[a,*], Yoko Tomioka[a], Eduard Vieta[a], Carla Torrent[a]

[a] *Barcelona Bipolar and Depressive Disorders Program, Institute of Neurosciences, University of Barcelona, IDIBAPS, CIBERSAM, Hospital Clinic of Barcelona, Catalonia, Spain*
[b] *Universidade Federal do Rio Grande do Sul (UFRGS), Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil*
[c] *Barcelona Clinic Schizophrenia Unit, Hospital Clinic of Barcelona, Neuroscience Institute, University of Barcelona, Catalonia, Spain*
[d] *Mental Health Group, IMIM (Institut Hospital del Mar d'Investigacions Mèdiques)-Hospital del Mar, CIBERSAM, Barcelona, Catalonia, Spain*

Received 18 October 2018; received in revised form 1 April 2019; accepted 23 April 2019

KEYWORDS
Bipolar disorder;
Functional remediation;
Psychoeducation;
BDNF;
Functioning

Abstract
The main aim of this study is to evaluate the impact of functional remediation (FR) in serum brain derived neurotrophic factor (BDNF) levels in euthymic adult patients with Bipolar Disorder (BD). A total of 128 participants were recruited at the Hospital Clinic of Barcelona. They were assessed at baseline and at the end of follow-up by the means of Hamilton Depression Scale (HAM-D), Young Mania Rating Scale (YMRS) and Functioning Assessment Short Test (FAST), as well as a clinical structured interview to collect clinical and demographic variables of interest. Blood samples were also collected to assess BDNF levels. After baseline assessment, patients received FR, Psychoeducation or treatment as usual (TAU).

* Corresponding author.
E-mail address: amartiar@clinic.ub.es (A. Martinez-Aran).
[1] First co-author.

https://doi.org/10.1016/j.euroneuro.2019.04.002

One hundred and two out of 126 participants finished the study distributed as follows: FR group ($n = 39$); Psychoeducation group ($n = 47$) and TAU group ($n = 16$). Longitudinal repeated-measures analyses addressing the treatment effect on BDNF levels showed non-significant differences between the three groups (Pillai's trace = 0.06; $F_{(2,97)} = 0.28$; $p = 0.75$), suggesting no interaction between treatment allocation and time on BDNF levels. The results of this study suggest that FR has no effect on peripheral BDNF levels in euthymic patients with BD, despite the improvement in psychosocial functioning.

1. Introduction

Bipolar disorder (BD) is a recurrent chronic mood disorder characterized by episodes of hypomania/mania and depression. It affects more than 1% of the world's population and together with other mental illnesses represents one of the main growing causes of chronicity and disability among young people leading to a rise in mortality rates, particularly death by suicide (Grande et al., 2016; Murray et al., 2012; Vieta et al., 2018a). Pharmacological treatment reduces symptoms, prevents further relapses and recurrences, but it is still not enough to recover patients from functional impairment (Vieta et al., 2013a, 2013b). FR is a novel therapy with proven effectiveness at improving psychosocial functioning in euthymic patients with BD. It is an intervention based on the training of neuropsychological skills (including attention, memory and executive functions) and the application of ecological exercises to improve real life functioning (Bonnin et al., 2016; Torrent et al., 2013); however, the biological correlates of this intervention (if any) remains still unknown.

The discovery of biomarkers in medicine has opened new horizons to the study of several illnesses, including mental disorders. It has been found decreased levels of BDNF in patients with BD during acute episodes when compared to controls (de Oliveira et al., 2009; Tramontina et al., 2007); however, BDNF levels do not differ from healthy controls during euthymia (Cunha et al., 2006). In this line, a systematic review and meta-analysis, which included a total of 1113 patients with BD, found that the peripheral BDNF levels were reduced both in the manic and depressive episodes but presented normal levels in euthymia and there was an increase of BDNF levels following treatment for acute mania (Fernandes et al., 2011). Moreover BDNF is one of the mediators explaining the concept of allostatic load (AL). This concept helps to explain the vulnerability to stress, cognitive impairment and physical comorbidity found in patients with BD (Kapczinski et al., 2008). Since BDNF is a protein involved in neuroplasticity and neurogenesis, it has been hypothesized that BDNF together with other neurotrophines could be involved in some structural changes described in BD, involving the amygdala, hippocampus and prefrontal cortex (Vieta et al., 2013b). In this regard, understanding the variations of BDNF levels and other neurotrophines during mood episodes or after receiving any pharmacological treatment could shed some light to validate the concept of AL. In this sense, at least two studies have reported an increase of BDNF levels in lithium responders compared to non-responders (de Sousa et al., 2011; Rybakowski, 2014). Other drugs such as ketamine (Grunebaum et al., 2017; Rybakowski et al., 2013) and other mood stabilizers including valproate (Chen et al., 2014) have also been found to increase BDNF levels, although not all the studies find significant changes (Cevher Binici et al., 2016).

When it comes to psychological treatments, literature is even scarcer, at least in the BD field. To the best of our knowledge, only one study has evaluated the changes in neurotrophines after a psychological treatment in patients with BD. Specifically, the authors found a significant increase of the Glial cell-derived neurotrophic factor (GDNF) between baseline and post combined psychoeducation (Wiener et al., 2017). There is also another ongoing study aiming at evaluate changes in BDNF after a mindfulness-based cognitive therapy vs. psychoeducation in a sample of patients with BD, but so far, no results are available (Lahera et al., 2014). In unipolar depression, another study (da Silva et al., 2018) also failed to find significant changes in neurotrophic factors (BDNF, beta-nerve growth factor, beta NGF and GDNF) in patients who received 16 sessions of CBT. Finally, in schizophrenia, Penadés and colleagues (Penadés et al., 2017) found that patients with Val66Met polymorphism, showed increased levels of BDNF in Val carriers after receiving cognitive remediation.

These findings reveal the need to analyze the possible existence of neuroprotective effects from certain psychological interventions used in the treatment of psychiatric diseases, including BD. The inclusion of biomarkers before and after a therapy intervention could help clinicians decide the best option treatment. In this line, research findings suggest that psychological interventions have measurable effects on the brain in addition to their "psychological impact" (Gabbard, 2000). Hence, the aim of this study was to evaluate BDNF changes after FR treatment when compared to psychoeducation and the Treatment as usual (TAU) group in euthymic patients. Because BDNF has a high expression in the brain areas involved in the regulation of cognition and emotion (Gorski et al., 2003) and FR is a therapy focused on the training of neurocognitive skills (Martínez-Arán et al., 2011), it is likely that BDNF levels improve in those patients who receive FR. Hence, we hypothesized that those patients in the FR group would increase BDNF serum levels after treatment when compared to psychoeducation or TAU. As secondary objectives, we assessed changes in mood symptoms and psychosocial functioning after FR versus the other interventions. Finally, as a tertiary objective, neurocognitive performance along follow-up was also investigated.

2. Experimental procedures

2.1. Design

This is a 6-months follow-up study to test the impact of FR as an add-on treatment to medication for patients with BD by assessing the differences in serum BDNF levels when compared to Psychoeducation and TAU group. It is a naturalistic cohort study, since patients were allocated in each group following clinical decision.

2.2. Participants

Participants in this study were recruited at the Barcelona Bipolar Disorders Program at the Hospital Clínic (University of Barcelona). It is a University based program providing integrated care for difficult-to-treat patients with BD from across Catalonia, as well as care to patients with BD from a specific catchment area in Barcelona (Vieta, 2011). The patients fulfilled the following inclusion criteria: (a) diagnosed with BD according to DSM-5 criteria (American Psychiatric Association, 2013), (b) assessed during euthymia, defined as Young Mania Rating Scale (YMRS) score ≤ 6 (Colom et al., 2002; Young et al., 1978) and Hamilton Depression Rating Scale-17 (HAM-D) score ≤ 8 (Cordero Villafáfila, 1986 and Ramos-Brieva; HAMILTON, 1960) and (c) aged between 18 and 65 years old. Exclusion criteria were: (a) current diagnosis of substance abuse or dependence; (b) history of mental retardation or any clinical condition that could interfere in the interview.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the ethics committee of the Hospital Clinic. All participants received extensive information on the study and provided written informed consent prior the inclusion.

2.3. Clinical assessments

After providing written informed consent, all participants went through a structured clinical interview of the Program's protocol based on the SCID for DSM-5 (American Psychiatric Association, 2013). Variables such as age, gender, diagnosis, the number and the type of episodes, chronicity (illness duration in years), number of hospitalizations, and history of psychosis were collected. All the information provided by the patients was verified by reviewing the clinical history of each patient.

After collecting the data, patients were assessed with several clinical scales: first, the HAM-D and the YMRS were administered to ensure that patients met criteria for euthymia at the time of study enrollment. Psychosocial functioning was assessed by means of the Functioning Assessment Short Test (FAST) (Rosa et al., 2007) an interviewer-administered instrument developed to assess the main difficulties in daily life of patients with BD. The global score is the addition of all the items of the scale. The FAST total score can range from 0 to 72 and higher scores indicate greater disability.

2.4. BDNF serum levels assessment

Ten milliliter samples of venous blood were collected into anticoagulant-free vacuum tubes. Blood samples were taken in the morning between 9:00 and 11:00 a.m.; patients were not required to be fasted before blood drawing. Blood was then centrifuged at 4000 g for 10 min and serum was separated and stored at $-80\,^{\circ}C$. Serum BDNF levels were measured by sandwich enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's instructions (R&D Systems, USA – Catalogue No. DBD00).

Microtiter plates (96-well flat-bottom) pre-coated with monoclonal antibody specific for human free BDNF were incubated for 2 h at room temperature with the samples and standard curve ranging from 62.5 to 2000 pg/mL of BDNF. Plates were then washed three times with wash buffer and Human Free BDNF Conjugate was added to all and incubated for 1 h at room temperature. After washing, incubation with substrate solution for 30 min at room temperature was carried out and after this time stop solution was added and the amount of BDNF was determined (absorbance set at 450 nm). The standard curve shows a direct relation between optical density and BDNF concentration. In addition, intra-assay and inter-assay coefficients of variation are $+3.8\%$ and $+11.3\%$, respectively. Tests were performed in duplicate and the investigator was blinded to the group allocation during the experiment.

2.5. Neuropsychological assessment

Patients receiving either TAU or FR were assessed using a comprehensive neuropsychological battery at baseline and at 6-months follow-up. This assessment involved different neurocognitive domains which are described as follows:

1) Estimated IQ was evaluated with the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997), vocabulary subtest. This measure was evaluated only at baseline.
2) The Processing Speed domain consisted of two subtest of the WAIS-III (Wechsler, 1997): the digit-symbol coding and the symbol search.
3) The Working Memory domain comprised the arithmetic, digits, and letter-number sequencing of the WAIS-III (Wechsler, 1997).
4) The verbal memory domain consisted of the California Verbal learning Test (CVLT) (Delis et al., 1987).
5) Executive functions were tested by several test assessing set shifting, planning, verbal fluencies, and response inhibition, namely the computerized version of the Wisconsin Card Sorting test (Heaton, 1981), the Stroop Color-Word Interference Test (SCWT) (Golden, 1978), the Trail Making Test -part B (TMT-B) (Reitan, 1958), phonemic fluency (F-A-S) and categorical fluency (animal naming), both components of the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1976).
6) Attention was measured with the Continuous Performance Test-II (CPT-II), version 5 (Conners, 2000) and with the Trail Making Test -part A (TMT-A) (Reitan, 1958)

2.6. Interventions

The FR program consists of 21 weekly sessions, each lasting 90 min. This intervention addresses neurocognitive issues such as attention, memory and executive functions; however it focuses even more on enhancing daily routine functioning. The content of the intervention is based on ecological tasks to be performed in the clinic as well as at home. Participants receive training with exercises for memory, attention, problem-solving and reasoning, multitasking and organization to improve their functional outcome. A manual of this intervention has been published (Vieta et al., 2014). The psychoeducation group also consisted of 21 weekly sessions of 90 min each, aimed at preventing recurrences of BD illness by improving five main issues: illness awareness, treatment adherence, early detection of prodromal symptoms of relapse, substance use avoidance, and lifestyle regularity (Colom and Vieta, 2006). In the TAU group, participants received prescribed pharmacological treatment without any adjunctive psychosocial therapy.

Table 1 Clinical and demographic characteristics.

Variables	Functional Remediation ($n=39$) Mean (SD) (A)	Psychoeducation ($n=47$) Mean (SD) (B)	TAU ($n=16$) Mean (SD) (C)	F (p)	Tukey post-hoc
Age	48,5 (6,3)	35,2 (9,2)	39,5 (9,9)	25,6 ($p<0,001$)	$A>B$,C
Years of education	14,9 (4,0)	14,3(2,7)	16,2 (5,1)	1,4 ($p=0,24$)	$A=B$,C
Estimated IQ	107,7 (8,3)	105,7 (7,7)	111,5 (7,4)	3,3 ($p=0,04$)	$A=B$, $C>B$
HAM-D total score	6,3 (3,5)	2,0 (2,2)	3,8 (3,3)	21,9 ($p<0,001$)	$A>B$,C
YMRS total score	1,6 (1,9)	1,2 (1,6)	0,8 (1,6)	1,3 ($p=0,27$)	$A=B$,C
FAST total score	34,5 (9,9)	15,5 (11,1)	19,9 (8,6)	34,6 ($p<0,001$)	$A>B$,C
Chronicity (years of illness)	21,6 (9,5)	11,5 (8,7)	15,1 (8,3)	14,5 ($p<0,001$)	$A>B$,C
Number of total episodes	12,3 (9,6)	9,7 (8,9)	6,4 (3,5)	1,2 ($p=0,31$)	$A=B$,C
Number of previous manic episodes	1,8 (2,5)	1,9 (2,0)	1,8 (1,3)	0,3 ($p=0,97$)	$A=B$,C
Number of previous depressive episodes	5,2 (5,9)	4,2 (4,4)	2,0 (1,7)	1,0 ($p=0,37$)	$A=B$,C
Number of previous hospitalizations	2,2 (2,1)	1,3 (1,4)	0,7 (0,7)	3,3 ($p=0,04$)	$A=B$,C
	n (%)	n (%)	n (%)	Chi (p)	
Gender (women)	10 (27)	22 (46,8)	5 (31,3)	3,7 ($p=0,15$)	
Diagnosis (Type I)	40 (85,1)	25 (65,8)	14 (82,4)	4,7 ($p=0,09$)	
Lifetime psychotic symptoms (yes)	21 (56,8)	35 (74,8)	9 (52,9)	3,9 ($p=0,31$)	

2.7. Statistical analyses

Demographic and clinical features at baseline and at follow-up were analyzed using ANOVA for continuous variables and chi square for categorical variables. These analyses were performed using the Statistical Package for Social Sciences version 20.0 (SPSS, Chicago, IL).

In order to test the main hypothesis, group x time effects overall BDNF levels were analyzed using repeated measures ANOVA comparing group differences at baseline and at six-months follow-up (after the intervention). This analysis only takes into account completed cases; consequently missing values due to of loss to follow-up were not included in the present analysis.

The second and third hypotheses regarding mood (HAM-D and YMRS), psychosocial functioning (FAST) and neuropsychological changes were also tested with the same analysis used for the main hypothesis. However, to assess the changes in neuropsychological performance, five different cognitive composites scores were created according to the cognitive domains assessed. First, all neurocognitive variables were standardized to z-scale scores. Then, the variables were grouped according to the neurocognitive domain assessed. In total, five composite scores were obtained: (1) the Processing Speed domain consisted of two variables derived from the two subtest of the WAIS-III (digit-symbol coding and symbol search); (2) the Working Memory domain consisted of three variables derived from the three subscales of the WAIS-III (arithmetic, digits and letter-number sequencing); (3) verbal memory composite domain consisted of five variables: the total trials 1–5 list A, short-delay free recall, short-delay cued recall, long-delay free recall and long-delay cued recall; (4) the executive functions composite score consisted of six variables: categories and perseverative errors of the WCST, SCWT interference, animal naming, phonemic fluency and TMT-B; (5) the attention composite score consisted of four variables: CPT-II omission errors, CPT-II commission errors, CPT detectability (*d'*) and TMT-A.

All analyses in this study were two-tailed with alpha set at $p<0.05$ and were performed with the Statistical Package for Social Sciences version 20.0.

3. Results

3.1. Demographic and clinical features

A total of 128 patients were recruited for this study. The distribution was made as follows: FR, $n=46$; Psychoeducation, $n=53$; TAU, $n=29$. After 6-months follow-up, a total of 102 patients were re-assessed (FR, $n=39$; Psychoeducation, $n=47$; TAU, $n=16$). Table 1 shows the data for patients who finished follow-up. As shown in the table, the three patient groups differed in some clinical and demographic variables at baseline. Patients in the FR group were older ($F_{(2,98)}=25.6$; $p<0.001$), presented higher scores in the HAM-D ($F_{(2,99)}=1.3$; $p<0.001$) and showed greater baseline functional impairment ($F_{(2,99)}=1.2$; $p<0.001$) when compared to the remaining groups.

At baseline, participants in the three groups were equivalent in terms of educational level, but estimated IQ was significantly higher in the TAU group when compared to the psychoeducation group ($F_{(2,99)}=1.2$; $p<0.001$). In terms of gender, diagnosis and lifetime psychotic symptoms patients were equally distributed across groups. Further details are shown in Table 1.

3.2. Longitudinal changes in BDNF

Longitudinal repeated-measures analyses addressing the effect of the treatment on BDNF levels showed non-significant

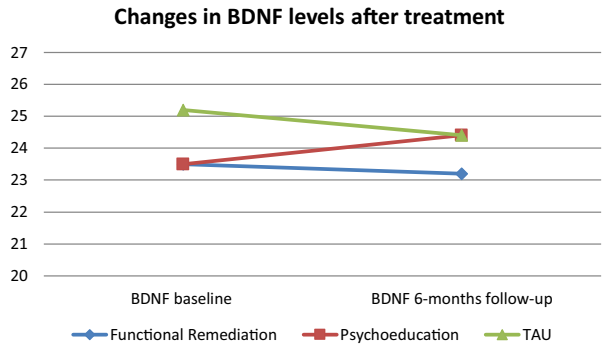


Fig. 1 BDNF levels pre and post treatment.

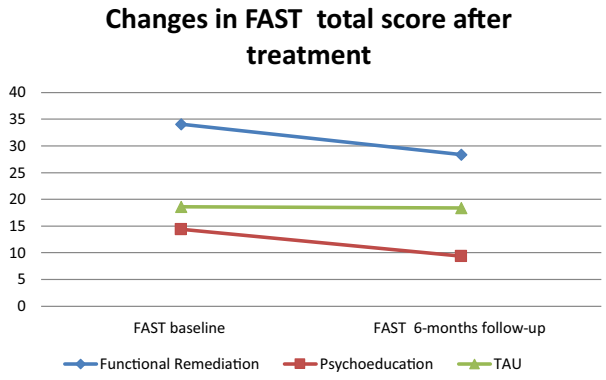


Fig. 2 FAST scores pre and post-treatment.

differences between the three groups (Pillai's trace = 0.06; $F_{(2,97)}$=0.28; p = 0.75), suggesting no interaction between treatment allocation and time (from baseline to 6-months follow-up) on BDNF levels. As shown in Fig. 1, patients allocated in the FR group did not differ significantly from patients allocated in the remaining groups.

Since baseline differences were detected in some variables, including subdepressive symptoms (HAM-D total score), psychosocial functioning (FAST total score) age and chronicity, we controlled for their potential confounding effects. Hence, four additional repeated-measures ANCOVA were performed in order to study the effect of these three variables on BDNF levels. According to the analyses, there was no significant interaction between time x subdepressive symptoms (Pillai's trace = 0.028; $F_{(1,93)}$=2.65; p = 0.10) and the interaction between treatment allocation and time remained non-significant (Pillai's trace = 0.024; $F_{(2,93)}$=1.15; P = 0.32). Regarding the effect of baseline psychosocial functioning, a significant interaction between time and baseline FAST total score (Pillai's trace = 0.04; $F_{(1,96)}$= 4.3; p = 0.04) was found, but there was no significant interaction between time x group treatment allocation (Pillai's trace= 0.03; $F_{(2,96)}$=1.65; p = 0.19). Finally, no significant effect of age was detected on BDNF levels neither on time (Pillai's trace=0.007; $F_{(1,94)}$=0.70; p = 0.40) or treatment allocation (Pillai's trace=0.012; $F_{(2,94)}$=0.55; p = 0.57). Chronicity (illness duration in years) did not affect either the BDNF levels and no significant effects were found after controlling for this confounding variable (Pillai's trace=0.012; $F_{(1,87)}$=0.50; p = 0.60) (Fig. 2).

3.3. Longitudinal changes in FAST total scores

Regarding the changes in the FAST scale, a significant interaction between treatment and time was found (Pillai's trace = 0.082; $F_{(2,88)}$=3.81; p = 0.026). When Tukey post hoc tests were performed, it was found that FR differed significantly from treatment as usual (p = 0.039), but fell short of significance when compared with psychoeducation (p = 0.94).

3.4. Longitudinal changes in mood

Concerning longitudinal changes in mood, both depressive and manic symptoms, no significant interaction was found between treatment allocation and time on HAM-D total (Pillai's trace=0.071; $F_{(2,70)}$=2.67; p = 0.074) score or on YMRS total score (Pillai's trace= 0.074; ($F_{(2,69)}$=2.75; p = 0.071). Table 2 summarizes the mean and standard deviations for the three groups in the main and secondary variables of the study.

3.5. Longitudinal changes in neuropsychological variables

Finally, when examining neurocognitive performance at follow-up, no significant interaction between treatment allocation x time were found in any of the composite cognitive domains assessed. See Table 3 for further details.

4. Discussion

To the best of our knowledge, this is the second study to investigate the effects of a psychological intervention on levels of peripheral BDNF compared with psychoeducation and TAU. Contrary to our main hypothesis, we found no statistically significant difference in BDNF levels between the patients who received FR vs. the remaining groups.

To date, there is only one published study assessing BDNF levels after another psychological intervention in BD. It is a randomized controlled trial assessing BDNF, GDNF and Nerve Growth Factor (NGF) serum levels after a brief psychoeducation intervention vs. treatment as usual (Wiener et al., 2017). They did not find any significant changes on BDNF nor NGF levels post intervention in any of the groups. Only GDNF serum levels increased significantly from baseline to follow-up in patients allocated in the psychoeducation group. The authors concluded that psychoeducation as an add-on therapy was effective at increasing GDNF levels in a sample of young adults with BD. Wiener's et al. (2017) study differs from our in some aspects: first, our study was not a randomized controlled trial; instead, we included a total of three arms of intervention and patients were allocated in each treatment arm according to clinical decision. Second, in Wiener's study, euthymia was not an inclusion criterion and patients were subsyndromic at baseline, presenting scores in the HAM-D around 12 and a score around 7 in the YMRS. Third, our patients were older in the three groups, especially when compared to those in the FR group. And finally,

Table 2 Longitudinal changes in main and secondary outcome variables.

Variables	Functional Remediation ($n = 39$) Mean (SD)		Psychoeducation ($n = 45$) Mean (SD)		TAU ($n = 16$) Mean (SD)	
	Baseline	6-months follow-up	Baseline	6-months follow-up	Baseline	6-months follow-up
BDNF serum levels (ng/ml)	23,51 (12,05)	23,22 (8,10)	23,53 (11,16)	24,42 (9,48)	25,22 (6,78)	24,45 (7,50)
FAST total score	34,06 (9,33)	28,03 (8,21)	14,37 (9,55)	9,34 (8,63)	18,59 (9,07)	18,45 (9,67)
HAM-D total score	6,11 (2,88)	5,47 (2,36)	2,07 (2,34)	1,56 (2,01)	3,20 (2,20)	5,50 (6,62)
YMRS total score	1,68 (1,73)	1,37 (1,67)	1,20 (1,70)	1,00 (1,65)	0,90 (2,02)	2,00 (2,05)

Table 3 Neuropsychological changes across time and functional remediation vs. TAU.

Variables	Functional remediation ($n = 27$)		TAU ($n = 12$) Mean (SD)		Group × time interaction Mean (SD)
	Baseline	6-months follow-up	Baseline	6-months follow-up	Pillai's trace (p)
Processing speed	0,05	−0,09	0,3	0,28	0,08 (0,60)
Working memory	0,16	0,05	−0,24	−0,14	0,001 (0,96)
Composite verbal memory score	−0,17	−0,14	0,44	0,37	0,007 (0,63)
Composite executive functioning score	−0,18	0,01	−0,1	0,06	0,001 (0,85)
Composite attention score	−0,48	−0,11	0,15	0,39	0,01 (0,61)

their psychological intervention was shorter than ours. Despite these differences, our results converge when it comes to invariability of BDNF serum levels after a psychological intervention.

There is another ongoing study in BD (Lahera et al., 2014) trying to find variations of BDNF levels associated to the different treatment arms (psychoeducation or mindfulness-based cognitive therapy) and its possible associations to neurospsychological variables. Nevertheless, no results have been published yet. Another study including a sample of patients with unipolar depression assessed the changes of BDNF and GDNF levels and severity of depressive symptoms in patients diagnosed with unipolar depression undergoing cognitive-behavioral therapy. The authors did not found significant correlations between the neurothrophines and changes in severity of depressive symptoms (da Silva et al., 2018).

In schizophrenia, two studies have evaluated the effect of a cognitive remediation therapy on BDNF serum levels. One found positive results (Vinogradov et al., 2009) while the other could not replicate the findings (Penadés et al., 2017). However, the latter study suggested that BDNF genetic variants could play a role in different response patterns of BDNF levels. They found that Val/Val carriers increased BDNF levels during a cognitive remediation, but not the Met carriers. Unfortunately, the present study did not assess these polymorphisms and we could not control for this variable. In regards to the only positive study so far carried out in schizophrenia (Vinogradov et al., 2009), the authors found a significant increase in BDNF serum levels 10 weeks after treatment. The intervention consisted of a computer training based on auditory and verbal processing. Aside from changes in BDNF, they also found a significant improvement in global cognition, however no correlation was found between increased BDNF and improved cognition. Thus, the significance of increased BDNF in relation to treatment success suggested that BDNF is not a biological correlate of cognitive improvement. In this line, the biological correlates of FR (if any) still remain unknown and other mechanisms beyond BDNF signaling should be investigated in order to elucidate this issue. The exhaustive FR intervention (21-weeks long) failed to change BDNF levels despite having found a significant improvement in psychosocial functioning. It is likely that FR alone is not enough to stimulate neurotrophic changes (in particular, BDNF) at least measured in serum levels.

In this line, one pilot study conducted in schizophrenia found that the combination of a program including physical exercise plus cognitive remediation could lead to an increase in BDNF serum levels (Nuechterlein et al., 2016) and a recent review (Campos et al., 2017) suggested that aerobic exercise preceding cognitive remediation may create a state of neuroplastic readiness in the brain through BDNF upregulation, which could potentiate the effectiveness of cognitive remediation. Therefore, it might be hypothesized that a combined program in BD including FR plus exercise could lead to increased neuroplasticity.

The higher baseline scores on the FAST scale and chronicity found in the FR group are noteworthy, indicating a worse psychosocial outcome in this group compared with the other

two. However, after controlling for these variables the results are not modified indicating a lack of association between chronicity (longer illness duration) and functional outcome with BDNF serum levels. This assumption is in line with a previous study that was conducted with patients who had suffered from BD for 23 years (in our FR group the mean chronicity is 21 years) (Barbosa et al., 2013) although recent studies have suggested that neuroplasticity may be negatively affected due to neuroprogressive changes that occur during the course of BD (Berk et al., 2011). In line with this, one study (Kauer-Sant'Anna et al., 2009) found an increase of BDNF levels in early stages of the illness, hence we cannot rule out a positive effect of the interventions in BDNF serum levels, if applied early after illness onset (Vieta et al., 2018b).

Despite failing to improve BDNF levels, the present study corroborates the positive results found in the randomized controlled trial where the efficacy of FR was tested (Torrent et al., 2013). In the original study, patients allocated in the FR group improved 6 points their total score in the FAST scale after treatment. In the present study, the mean increase was 5.7, similar to the first study. The significant difference in functioning as found when FR was compared to TAU but not when compared to the psychoeducation group, which is also in line with the study efficacy.

Lastly, in line with previous literature, no significant changes in mood across treatment groups were found (Bonnin et al., 2016; Torrent et al., 2013), confirming no effect of FR or Psychoeducation on mood symptoms. Given that patients were euthymic when included in the study and remained stable, it is unlikely to find significant results regarding these variables. As stated in a previous report (Fernandes et al., 2011) the lack of significant differences in euthymic patients with BD may further support the hypothesis that BDNF might be proposed as a state -rather than a trait marker for BD. Regarding neuropsychological performance, we did not find any significant changes in the group allocated in FR compared to TAU after 6-months follow-up, which is in line with the original trial testing the efficacy of the intervention (Torrent et al., 2013). So far, one study, with longer follow-up, found significant improvement in verbal memory, suggesting that changes in neurocognition may occur with certain delay or as a result of an accumulative effect (Bonnin et al., 2016). This might explain that neither our study or other cross-sectional reports (Chou et al., 2012; Dias et al., 2009) found no association between neurocognition and serum BDNF levels. Maybe more individualized interventions should be taken into account according to patients' functioning profile (Solé et al., 2018).

This study has several limitations. First, the small sample size of the groups may limit the detection of differences in BDNF outcomes, and a type II error (false negative) cannot be completely rule out. Second, this study was not a randomized controlled trial and patients were not equally distributed in some confounding variables that were not gathered, including BMI and smoking status. Third, it is possible that no effects were observed in our study because the pharmacological treatment could have changed throughout the evaluations in some participants. Nevertheless, this is a consequence of the naturalistic design of this project in which participants maintained or changed their usual treatment according to the guidelines for BD. Another possible explanation for this negative finding could be due to the method used to detect changes in BDNF levels; we have measurements of serum BDNF levels but not from central nervous system levels. Finally, the lack of genetic assessment of BDNF Val66Met polymorphism was not assessed and it is known to have a significant role in BDNF plasma levels.

Despite these limitations, the results of our study suggest that FR and Psychoeducation failed to change BDNF serum levels in euthymic patients with BD. To the best of our knowledge this is the second study in the BD field assessing changes in this neurotrophine and, so far, both studies have presented negative results. Research of biological correlates in BD is still immature and deserves further attention; it may be likely that BDNF is not the only mediator involved in the complex process of neural plasticity. Other variables such as an early exposure to traumatic life events and posttraumatic stress disorder have been found to have an impact in the stress response alterations (Grande et al., 2010) which in turn, regulates the BDNF production. Maybe more trauma-orientated interventions could be effective to observe changes in BDNF. As pointed by Penadés et al. (2017) it might be possible that BDNF changes depend on genetic variants that we might have missed. For instance, Grande et al. (2014) found a differential change in peripheral levels of BDNF along the treatment of BD depending on their genotype. Finally, if the ultimate objective is to stimulate neuroplasticity and neurogenesis it would be interesting to study a combination program consisting of FR and exercise since preliminary studies in schizophrenia has shown positive results (Nuechterlein et al., 2016).

Acknowledgments

Dr. Bonnin would like to thank the Department de Salut de la Generalitat de Catalunya for its support through a PERIS grant (SLT002/16/00331). Dr. Carla Torrent is funded by the Spanish Ministry of Economy and Competitiviness, Instituto Carlos III, through a 'Miguel Servet' postdoctoral contract (CPI14/00175).

Conflict of interest

The authors declare no conflict of interest related to this manuscript.

Contributors

All authors contributed to and have approved the final manuscript

Role of funding source

This study has been funded by Instituto de Salud Carlos III through the project "PI12/01498, PI15/00330" integrated into the Plan Nacional de I+D+I (Co-funded by European Regional Development Fund/European Social Fund) "Investing in your future"). CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la

Generalitat de Catalunya to the Bipolar Disorders Group (2017 SGR 1365) and the CERCA Programme/Generalitat de Catalunya. This work has also been supported with the project SLT006/17/00357, in the "Pla estratègic de Recerca i Innovació en Salut 2016-2020" (Health Department). CERCA Programme/Generalitat de Catalunya). Dr Martinez-Aran's project is supported, in part, by a 2013 NARSAD, Independent Investigator Grant from the Brain & Behavior Research Foundation (Grant number: 20288).

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (5th ed.).

Barbosa, I.G., Rocha, N.P., Miranda, A.S.de, Huguet, R.B., Bauer, M.E., Reis, H.J., Teixeira, A.L., 2013. Increased BDNF levels in long-term bipolar disorder patients. Rev. Bras. Psiquiatr. 35, 67–69.

Benton, A., Hamsher, K., 1976. Multilingual Aphasia Examination. University of Iowa, Iowa City, IA.

Berk, M., Kapczinski, F., Andreazza, A.C., Dean, O.M., Giorlando, F., Maes, M., Yücel, M., Gama, C.S., Dodd, S., Dean, B., Magalhães, P.V.S., Amminger, P., McGorry, P., Malhi, G.S., 2011. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 35, 804–817. doi:10.1016/j.neubiorev.2010.10.001.

Bonnin, C.M., Torrent, C., Arango, C., Amann, B.L., Sole, B., Gonzalez-Pinto, A., Crespo, J.M., Tabares-Seisdedos, R., Reinares, M., Ayuso-Mateos, J.L., Garcia-Portilla, M.P., Ibanez, A., Salamero, M., Vieta, E., Martinez-Aran, A.CIBERSAM Functional Remediation Group, 2016. Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. Br. J. Psychiatry 208, 87–93. doi:10.1192/bjp.bp.114.162123.

Campos, C., Rocha, N.B., Lattari, E., Nardi, A.E., Machado, S., 2017. 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 16, 638–651. doi:10.2174/1871527315666161223142918.

Cevher Binici, N., Inal Emiroğlu, F.N., Resmi, H., Ellidokuz, H., 2016. Serum brain-derived neurotrophic factor levels among euthymic adolescents with bipolar disorder type I. Noropsikiyatri Ars. 53, 267–271. doi:10.5152/npa.2015.8832.

Chen, S.-L., Lee, S.-Y., Chang, Y.-H., Chen, P.-S., Lee, I.-H., Wang, T.-Y., Chen, K.-C., Yang, Y.-K., Hong, J.-S., Lu, R.-B., 2014. Therapeutic effects of add-on low-dose dextromethorphan plus valproic acid in bipolar disorder. Eur. Neuropsychopharmacol. 24, 1753–1759. doi:10.1016/j.euroneuro.2014.09.001.

Chou, Y.-H., Wang, S.-J., Lirng, J.-F., Lin, C.-L., Yang, K.-C., Chen, C.-K., Yeh, C.-B., Liao, M.-H., 2012. Impaired cognition in bipolar I disorder: the roles of the serotonin transporter and brain-derived neurotrophic factor. J. Affect. Disord. 143, 131–137. doi:10.1016/j.jad.2012.05.043.

Colom, F., Vieta, E., 2006. Psychoeducation Manual for Bipolar Disorder. Cambridge University Press.

Colom, F., Vieta, E., Martínez-Arán, A., Garcia-Garcia, M., Reinares, M., Torrent, C., Goikolea, J.M., Banús, S., Salamero, M., 2002. Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale. Med. Clin. 119, 366–371.

Conners, C. (2000), Conner's Continuous Performances Test for Windows (CPT-II).

Cordero Villafáfila, A., Ramos-Brieva, J.A., 1986. Factor structure of the Castillian version of the Hamilton rating scale for depression. Actas Luso. Esp. Neurol. Psiquiatr. Cienc. Afines 14, 339–342.

Cunha, A.B.M., Frey, B.N., Andreazza, A.C., Goi, J.D., Rosa, A.R., Gonçalves, C.A., Santin, A., Kapczinski, F., 2006. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci. Lett. 398, 215–219. doi:10.1016/j.neulet.2005.12.085.

da Silva, S.K., Wiener, C., Ghisleni, G., Oses, J.P., Jansen, K., Molina, M.L., Silva, R., Souza, L.D., 2018. Effects of cognitive-behavioral therapy on neurotrophic factors in patients with major depressive disorder. Braz. J. Psychiatry 40, 361–366. doi:10.1590/1516-4446-2017-2357.

de Oliveira, G.S., Ceresér, K.M., Fernandes, B.S., Kauer-Sant'Anna, M., Fries, G.R., Stertz, L., Aguiar, B., Pfaffenseller, B., Kapczinski, F., 2009. Decreased brain-derived neurotrophic factor in medicated and drug-free bipolar patients. J. Psychiatr. Res. 43, 1171–1174. doi:10.1016/j.jpsychires.2009.04.002.

de Sousa, R.T., van de Bilt, M.T., Diniz, B.S., Ladeira, R.B., Portela, L.V, Souza, D.O., Forlenza, O.V, Gattaz, W.F., Machado-Vieira, R., 2011. Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study. Neurosci. Lett. 494, 54–56. doi:10.1016/j.neulet.2011.02.054.

Delis, D.C., Kramer, J.H., Kaplan, E.O.B., 1987. California Verbal Learning Test. Psychological Corporation, New York, NY.

Dias, V.V., Brissos, S., Frey, B.N., Andreazza, A.C., Cardoso, C., Kapczinski, F., 2009. Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder. Bipolar Disord. 11, 663–671. doi:10.1111/j.1399-5618.2009.00733.x.

Fernandes, B.S., Gama, C.S., Ceresér, K.M., Yatham, L.N., Fries, G.R., Colpo, G., de Lucena, D., Kunz, M., Gomes, F.A., Kapczinski, F., 2011. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J. Psychiatr. Res. 45, 995–1004. doi:10.1016/j.jpsychires.2011.03.002.

Gabbard, G.O., 2000. A neurobiologically informed perspective on psychotherapy. Br. J. Psychiatry 177, 117–122.

Golden, C., 1978. Stroop Color and Word Test. Stoelting, Chicago, IL.

Gorski, J.A., Zeiler, S.R., Tamowski, S., Jones, K.R., 2003. Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. J. Neurosci. 23, 6856–6865.

Grande, I., Berk, M., Birmaher, B., Vieta, E., 2016. Bipolar disorder. Lancet 387, 1561–1572. doi:10.1016/S0140-6736(15)00241-X.

Grande, I., Fries, G.R., Kunz, M., Kapczinski, F., 2010. The role of BDNF as a mediator of neuroplasticity in bipolar disorder. Psychiatry Investig. 7, 243. doi:10.4306/pi.2010.7.4.243.

Grande, I., Magalhães, P.V.S., Chendo, I., Stertz, L., Fries, G.R., Cereser, K.M., Cunha, Â.B.M., Gói, P., Kunz, M., Udina, M., Martín-Santos, R., Frey, B.N., Vieta, E., Kapczinski, F., 2014. Val66Met polymorphism and serum brain-derived neurotrophic factor in bipolar disorder: an open-label trial. Acta Psychiatr. Scand. 129, 393–400. doi:10.1111/acps.12192.

Grunebaum, M.F., Ellis, S.P., Keilp, J.G., Moitra, V.K., Cooper, T.B., Marver, J.E., Burke, A.K., Milak, M.S., Sublette, M.E., Oquendo, M.A., Mann, J.J., 2017. Ketamine versus midazolam in bipolar depression with suicidal thoughts: a pilot midazolam-controlled randomized clinical trial. Bipolar Disord. 19, 176–183. doi:10.1111/bdi.12487.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Heaton, R.K., 1981. Wisconsin Card Sorting Test Manual. Psychological Asessment Resources, Odessa, FL.

Kauer-Sant'Anna, M., Kapczinski, F., Andreazza, A.C., Bond, D.J., Lam, R.W., Young, L.T., Yatham, L.N., 2009. Brain-derived neurotrophic factor and inflammatory markers in patients with

early- vs. late-stage bipolar disorder. Int. J. Neuropsychopharmacol. 12, 447–458. doi:10.1017/S1461145708009310.

Kapczinski, F., Vieta, E., Andreazza, A.C., Frey, B.N., Gomes, F.A., Tramontina, J., Kauer-Sant'anna, M., Grassi-Oliveira, R., Post, R.M., 2008. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci. Biobehav. Rev. 32 (4), 675–692. doi:10.1016/j.neubiorev.2007.10.005.

Lahera, G., Bayón, C., Fe Bravo-Ortiz, M., Rodríguez-Vega, B., Barbeito, S., Sáenz, M., Avedillo, C., Villanueva, R., Ugarte, A., González-Pinto, A., de Dios, C., 2014. Mindfulness-based cognitive therapy versus psychoeducational intervention in bipolar outpatients with sub-threshold depressive symptoms: a randomized controlled trial. BMC Psychiatry 14, 215. doi:10.1186/s12888-014-0215-x.

Martínez-Arán, A., Torrent, C., Solé, B., Bonnín, C.M., Rosa, A.R., Sánchez-Moreno, J., Vieta, E., 2011. Functional remediation for bipolar disorder. Clin. Pract. Epidemiol. Mental Health 7, 112–116. doi:10.2174/1745017901107010112.

Murray, C.J.L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A.D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J.A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S.Y., Ali, M.K., AlMazroa, M.A., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Bahalim, A.N., Barker-Collo, S., Barrero, L.H., Bartels, D.H., Basáñez, M.-G., Baxter, A., Bell, M.L., Benjamin, E.J., Bennett, D., Bernabé, E., Bhalla, K., Bhandari, B., Bikbov, B., Abdulhak, A.Bin, Birbeck, G., Black, J.A., Blencowe, H., Blore, J.D., Blyth, F., Bolliger, I., Bonaventure, A., Boufous, S., Bourne, R., Boussinesq, M., Braithwaite, T., Brayne, C., Bridgett, L., Brooker, S., Brooks, P., Brugha, T.S., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Buckle, G., Budke, C.M., Burch, M., Burney, P., Burstein, R., Calabria, B., Campbell, B., Canter, C.E., Carabin, H., Carapetis, J., Carmona, L., Cella, C., Charlson, F., Chen, H., Cheng, A.T.-A., Chou, D., Chugh, S.S., Coffeng, L.E., Colan, S.D., Colquhoun, S., Colson, K.E., Condon, J., Connor, M.D., Cooper, L.T., Corriere, M., Cortinovis, M., de Vaccaro, K.C., Couser, W., Cowie, B.C., Criqui, M.H., Cross, M., Dabhadkar, K.C., Dahiya, M., Dahodwala, N., Damsere-Derry, J., Danaei, G., Davis, A., Leo, D.De, Degenhardt, L., Dellavalle, R., Delossantos, A., Denenberg, J., Derrett, S., Des Jarlais, D.C., Dharmaratne, S.D., Dherani, M., Diaz-Torne, C., Dolk, H., Dorsey, E.R., Driscoll, T., Duber, H., Ebel, B., Edmond, K., Elbaz, A., Ali, S.E., Erskine, H., Erwin, P.J., Espindola, P., Ewoigbokhan, S.E., Farzadfar, F., Feigin, V., Felson, D.T., Ferrari, A., Ferri, C.P., Fèvre, E.M., Finucane, M.M., Flaxman, S., Flood, L., Foreman, K., Forouzanfar, M.H., Fowkes, F.G.R., Fransen, M., Freeman, M.K., Gabbe, B.J., Gabriel, S.E., Gakidou, E., Ganatra, H.A., Garcia, B., Gaspari, F., Gillum, R.F., Gmel, G., Gonzalez-Medina, D., Gosselin, R., Grainger, R., Grant, B., Groeger, J., Guillemin, F., Gunnell, D., Gupta, R., Haagsma, J., Hagan, H., Halasa, Y.A., Hall, W., Haring, D., Haro, J.M., Harrison, J.E., Havmoeller, R., Hay, R.J., Higashi, H., Hill, C., Hoen, B., Hoffman, H., Hotez, P.J., Hoy, D., Huang, J.J., Ibeanusi, S.E., Jacobsen, K.H., James, S.L., Jarvis, D., Jasrasaria, R., Jayaraman, S., Johns, N., Jonas, J.B., Karthikeyan, G., Kassebaum, N., Kawakami, N., Keren, A., Khoo, J.-P., King, C.H., Knowlton, L.M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Laden, F., Lalloo, R., Laslett, L.L., Lathlean, T., Leasher, J.L., Lee, Y.Y., Leigh, J., Levinson, D., Lim, S.S., Limb, E., Lin, J.K., Lipnick, M., Lipshultz, S.E., Liu, W., Loane, M., Ohno, S.L., Lyons, R., Mabweijano, J., MacIntyre, M.F., Malekzadeh, R., Mallinger, L., Manivannan, S., Marcenes, W., March, L., Margolis, D.J., Marks, G.B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B.M., McAnulty, J.H., McDermott, M.M., McGill, N., McGrath, J., Medina-Mora, M.E., Meltzer, M., Memish, Z.A., Mensah, G.A., Merriman, T.R., Meyer, A.-C., Miglioli, V., Miller, M., Miller, T.R., Mitchell, P.B., Mock, C., Mocumbi, A.O., Moffitt, T.E., Mokdad, A.A., Monasta, L., Montico, M., Moradi-Lakeh, M., Moran, A., Morawska, L., Mori, R., Murdoch, M.E., Mwaniki, M.K., Naidoo, K., Nair, M.N., Naldi, L., Narayan, K.M.V., Nelson, P.K., Nelson, R.G., Nevitt, M.C., Newton, C.R., Nolte, S., Norman, P., Norman, R., O'Donnell, M., O'Hanlon, S., Olives, C., Omer, S.B., Ortblad, K., Osborne, R., Ozgediz, D., Page, A., Pahari, B., Pandian, J.D., Rivero, A.P., Patten, S.B., Pearce, N., Padilla, R.P., Perez-Ruiz, F., Perico, N., Pesudovs, K., Phillips, D., Phillips, M.R., Pierce, K., Pion, S., Polanczyk, G.V, Polinder, S., Pope, C.A., Popova, S., Porrini, E., Pourmalek, F., Prince, M., Pullan, R.L., Ramaiah, K.D., Ranganathan, D., Razavi, H., Regan, M., Rehm, J.T., Rein, D.B., Remuzzi, G., Richardson, K., Rivara, F.P., Roberts, T., Robinson, C., De Leòn, F.R., Ronfani, L., Room, R., Rosenfeld, L.C., Rushton, L., Sacco, R.L., Saha, S., Sampson, U., Sanchez-Riera, L., Sanman, E., Schwebel, D.C., Scott, J.G., Segui-Gomez, M., Shahraz, S., Shepard, D.S., Shin, H., Shivakoti, R., Silberberg, D., Singh, D., Singh, G.M., Singh, J.A., Singleton, J., Sleet, D.A., Sliwa, K., Smith, E., Smith, J.L., Stapelberg, N.J., Steer, A., Steiner, T., Stolk, W.A., Stovner, L.J., Sudfeld, C., Syed, S., Tamburlini, G., Tavakkoli, M., Taylor, H.R., Taylor, J.A., Taylor, W.J., Thomas, B., Thomson, W.M., Thurston, G.D., Tleyjeh, I.M., Tonelli, M., Towbin, J.A., Truelsen, T., Tsilimbaris, M.K., Ubeda, C., Undurraga, E.A., van der Werf, M.J., van Os, J., Vavilala, M.S., Venketasubramanian, N., Wang, M., Wang, W., Watt, K., Weatherall, D.J., Weinstock, M.A., Weintraub, R., Weisskopf, M.G., Weissman, M.M., White, R.A., Whiteford, H., Wiebe, N., Wiersma, S.T., Wilkinson, J.D., Williams, H.C., Williams, S.R., Witt, E., Wolfe, F., Woolf, A.D., Wulf, S., Yeh, P.-H., Zaidi, A.K., Zheng, Z.-J., Zonies, D., Lopez, A.D., 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 2197–2223. doi:10.1016/S0140-6736(12)61689-4.

Nuechterlein, K.H., Ventura, J., McEwen, S.C., Gretchen-Doorly, D., Vinogradov, S., Subotnik, K.L., 2016. Enhancing cognitive training through aerobic exercise after a first schizophrenia episode: theoretical conception and pilot study. Schizophr. Bull. 42 (Suppl 1), S44–S52. doi:10.1093/schbul/sbw007.

Penadés, R., López-Vílchez, I., Catalán, R., Arias, B., González-Rodríguez, A., García-Rizo, C., Masana, G., Ruíz, V., Mezquida, G., Bernardo, M., 2017. BDNF as a marker of response to cognitive remediation in patients with schizophrenia: a randomized and controlled trial. Schizophr. Res. doi:10.1016/j.schres.2017.12.002.

Reitan, R., 1958. Validity of the railmaking test as a indication of organic brain damage. Percept. Motor Skills 8, 271–276.

Rosa, A.R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2007. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin. Pract. Epidemiol. Mental Health 3, 5. doi:10.1186/1745-0179-3-5.

Rybakowski, J.K., 2014. Factors associated with lithium efficacy in bipolar disorder. Harv. Rev. Psychiatry 22, 353–357. doi:10.1097/HRP.0000000000000006.

Rybakowski, J.K., Permoda-Osip, A., Skibinska, M., Adamski, R., Bartkowska-Sniatkowska, A., 2013. Single ketamine infusion in bipolar depression resistant to antidepressants: are neurotrophins involved? Hum. Psychopharmacol. 28, 87–90. doi:10.1002/hup.2271.

Solé, B., Bonnin, C.M., Jiménez, E., Torrent, C., Torres, I., Varo, C., Valls, E., Montejo, L., Gómez-Ocaña, C., Tomioka, Y., Vieta, E., Martinez-Aran, A., Reinares, M., 2018. Heterogeneity of functional outcomes in patients with bipolar disorder: a cluster-analytic approach. Acta Psychiatr. Scand. 137, 516–527. doi:10.1111/acps.12871.

Torrent, C., Bonnin, C.del M., Martínez-Arán, A., Valle, J., Amann, B.L., González-Pinto, A., Crespo, J.M., Ibáñez, Á., Garcia-Portilla, M.P., Tabarés-Seisdedos, R., Arango, C., Colom, F., Solé, B., Pacchiarotti, I., Rosa, A.R., Ayuso-Mateos, J.L., Anaya, C., Fernández, P., Landín-Romero, R., Alonso-Lana, S., Ortiz-Gil, J., Segura, B., Barbeito, S., Vega, P., Fernández, M., Ugarte, A., Subirà, M., Cerrillo, E., Custal, N., Menchón, J.M., Saiz-Ruiz, J., Rodao, J.M., Isella, S., Alegría, A., Al-Halabi, S., Bobes, J., Galván, G., Saiz, P.A., Balanzá-Martínez, V., Selva, G., Fuentes-Durá, I., Correa, P., Mayoral, M., Chiclana, G., Merchan-Naranjo, J., Rapado-Castro, M., Salamero, M., Vieta, E., 2013. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. Am. J. Psychiatry 170, 852–859. doi:10.1176/appi.ajp.2012.12070971.

Tramontina, J., Frey, B.N., Andreazza, A.C., Zandona, M., Santin, A., Kapczinski, F., 2007. Val66met polymorphism and serum brain-derived neurotrophic factor levels in bipolar disorder. Mol. Psychiatry 12, 230–231. doi:10.1038/sj.mp.4001941.

Vieta, E., 2011. Bipolar units and programmes: are they really needed? World Psychiatry 10, 152.

Vieta, E., Berk, M., Schulze, T.G., Carvalho, A.F., Suppes, T., Calabrese, J.R., Gao, K., Miskowiak, K.W., Grande, I., 2018a. Bipolar disorders. Nat. Rev. Dis. Prim. 4, 18008. doi:10.1038/nrdp.2018.8.

Vieta, E., Langosch, J.M., Figueira, M.L., Souery, D., Blasco-Colmenares, E., Medina, E., Moreno-Manzanaro, M., Gonzalez, M.A., Bellivier, F., 2013a. Clinical management and burden of bipolar disorder: results from a multinational longitudinal study (WAVE-bd). Int. J. Neuropsychopharmacol. 16, 1719–1732. doi:10.1017/S1461145713000278.

Vieta, E., Salagre, E., Grande, I., Carvalho, A.F., Fernandes, B.S., Berk, M., Birmaher, B., Tohen, M., Suppes, T., 2018b. Early intervention in bipolar disorder. Am. J. Psychiatry 175, 411–426. doi:10.1176/appi.ajp.2017.17090972.

Vieta, E., Torrent, C., Martínez-Arán, A., 2014. Functional Remediation for Bipolar Disorder. Cambridge University Press.

Vieta, E., Popovic, D., Rosa, A.R., Solé, B, Grande, I., Frey, B.N., Martinez-Aran, A., Sanchez-Moreno, J., Balanzá-Martínez, V., Tabarés-Seisdedos, R., Kapczinski, F., 2013b. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Eur. Psychiatry 28, 21–29. doi:10.1016/j.eurpsy.2011.11.007.

Vinogradov, S., Fisher, M., Holland, C., Shelly, W., Wolkowitz, O., Mellon, S.H., 2009. Is serum brain-derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia? Biol. Psychiatry 66, 549–553. doi:10.1016/j.biopsych.2009.02.017.

Wechsler, D., 1997. The Wechsler Adult Intelligence Scale- III (WAIS-III).

Wiener, C.D., Molina, M.L., Moreira, F.P., dos Passos, M.B., Jansen, K., da Silva, R.A., de Mattos Souza, L.D., Oses, J.P., 2017. Brief psychoeducation for bipolar disorder: evaluation of trophic factors serum levels in young adults. Psychiatry Res. 257, 367–371. doi:10.1016/j.psychres.2017.07.062.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.