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Original article

High BDNF serum levels are associated to good cognitive functioning in bipolar disorder

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ABSTRACT

Background: Neurotrophins such as brain-derived neurotrophic factor (BDNF), inflammation and oxidative damage may contribute to the pathophysiology of bipolar disorder (BD) in terms of illness activity. To date, there is a lack of studies linking the cognitive impairment observed in BD with these neurobiological mechanisms. This study aimed to investigate the role of these neurobiological factors in clinical and cognitive outcomes in a sample of bipolar individuals.
Methods: We measured serum BDNF, cytokines and oxidative stress markers in a sample of 133 individuals: 52 euthymic bipolar patients, 32 manic patients and 49 healthy controls. They were all assessed with a comprehensive cognitive battery. Sociodemographic and clinical data were collected. Multiple linear regression models were built to study associations of neurotrophins and inflammatory and oxidative measures with cognitive functioning.
Results: BDNF levels were decreased in euthymic ($p = 0.039$) and manic ($p < 0.001$) individuals. Conversely, inflammatory (interleukin 6 (IL-6)) ($p = 0.019$) and oxidative stress ($p = 0.003$) measures were increased in bipolar individuals compared to controls. BDNF levels were associated with executive functioning ($\beta = 0.01$, $p = 0.02$) and verbal memory ($\beta = 0.013$, $p = 0.005$), together with other demographic variables. In particular, verbal memory was also associated with obesity (β=-0.04, $p = 0.005$). Neither inflammatory markers, oxidative stress markers nor other relevant clinical variables showed any association with cognitive outcome.
Conclusions: Of all the peripheral neurobiological factors analysed, BDNF was the only one significantly associated with cognitive dysfunction in bipolar disorder individuals. This study emphasizes the role of BDNF not only across mood phases but also in cognitive functioning.

1. Introduction

Bipolar disorder (BD) is a recurrent mood disorder affecting 1–3% of the world population [1]. It has a long-term outcome with incomplete recovery between episodes, cognitive impairment, and functional decline [1–6]. Its chronic course is associated with high rates of morbidity and mortality, making bipolar disorder one of the main causes of disability among young and working-age people [7]. Cognitive dysfunction is the key feature of functional impairment throughout periods of mania, depression and euthymia in BD [8].

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The neurobiological underpinnings of cognitive dysfunction remain unknown in psychiatric disorders [9]. Cognition is affected by a range of medical issues and neurochemical mechanisms [10]. There is evidence that endocrine (such as obesity) and cardiovascular issues which are more common in BD than in general population [11,12], may be negatively associated with cognitive progression [13,14].

Cognition is better understood in terms of complex networks operating over multiple temporal scales and incorporating various dimensions: from cellular cascades to cerebral circuits and, ultimately, society [9]. Moreover, a diverse palette of neuromodulators including acetylcholine, cytokines and neurotrophic proteins such as brain-derived neurotrophic factor (BDNF) influence cognitive performance [9]. In the same line, there are some neurobiological factors such as BDNF, immune-inflammatory and oxidative stress markers that have been consistently reported to be associated with brain structure and function and to be relevant to physiological and pathological neurodevelopment [15,16]. Associations between alterations in these systems have been reliably described in children and adults, across different mental disorders [17,18]. In particular, compelling evidence about these neurobiological factors in bipolar disorder has been found [19–21]. Indeed, several pathophysiological mechanisms have been proposed and investigated, to understand the interaction between these neurobiological factors and mood symptomatology in BD [16,22,23]. However, significantly less investigation has been conducted to elucidate the effect of inflammation, oxidative stress and neuroplasticity on cognition in BD [24,25].

The main aim of the current study was to investigate the association of cognitive performance with neuroprotective and neurodegenerative mechanisms (neurotrophins, and inflammation and oxidative stress markers) in patients with BD. We hypothesized that (1) bipolar individuals (euthymic and manic) would display a different pattern of BDNF, inflammatory-cytokine and oxidative stress markers as compared to healthy controls; and (2) cognitive performance would be associated with these neurobiological factors regardless of mood state.

2. Methods

2.1. Participants

A total of 133 individuals were enrolled in the study: 49 healthy controls, 52 euthymic bipolar and 32 manic bipolar individuals. All of them were evaluated by clinical interview with a psychiatrist, and underwent neuropsychological and biochemical tests.

Euthymic bipolar patients were recruited from the Outpatient Lithium Clinic at Hospital Universitari Santa Maria, Lleida, from 2003 until 2011. All of them met Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria for BD, as was determined by a Psychiatrist using the Structured Clinical Interview for Axis I Disorders [26]. They were aged between 18 and 65 years old. Euthymia state was determined when bipolar individuals obtained a total 17-item Hamilton Rating Scale for Depression (HAMD) [27] score below 8 and a total Young Mania Rating Scale (YMRS) [28] score below 6 for at least 3 months prior to the assessment [29]. Significant non-psychiatric illness, substance abuse or dependence or electroconvulsive therapy during the preceding year, were the exclusion criteria.

Manic bipolar patients were recruited from the Inpatient Psychiatric Unit, at Hospital Universitari Santa Maria, Lleida, during a manic phase, from 2012 until 2014. Inclusion and exclusion criteria were the same as for euthymic patients, except for the criteria of clinical stability: manic patients were included if they had a total score of 14 or above in the YMRS [30]. Blood extraction was performed at the beginning of the hospitalization in the acute phase of the disorder. Cognitive assessment was performed just prior to discharge when major manic symptoms were partially remitted, in order to guarantee collaboration of manic patients, without biasing cognitive performance, even though it meant gathering information at two separate points in time.

Forty-nine healthy controls were enrolled with advertisements and from non-medical hospital staff. Controls had no current or past psychiatric history, as determined by the Structured Clinical Interview for DMS-IV Axis I Disorders [26]. Additionally, healthy subjects were excluded if there was a family history of any Axis I disorder in a first-degree relative. Healthy subjects underwent the same exclusion criteria as the patients, and were assessed at the same full clinical and demographics interview by a trained psychiatrist. The Local Ethics Committee approved the study and written informed consent was obtained from all participants.

2.2. Demographic, clinical and pharmacological data

Demographic variables included age, gender, years of education and current work status. Body mass index (BMI) was also calculated for each participant. The established criteria for BMI were: normal weight, BMI of 18.5–24.9 kg/m^2; overweight, BMI of 25.0–29.9 kg/m^2; and obese, BMI > 30 kg/m^2 (National Heart LaBI NI of D and D and KD [31]. Psychiatric variables were obtained from the sample of bipolar patients, including: age at onset of illness, number of prior manic episodes and hospitalizations, period of stabilization (years), history of psychotic symptoms, seasonal pattern, suicide attempts and bipolar subtype (I or II) during the psychiatric interview. Other physical and medical issues (e.g. cardiovascular, neurological, gastrointestinal, haematological, renal, hepatic, respiratory or endocrine illnesses) and concurrent psychiatric and non-psychiatric medications were recorded in the same interview. Biochemical tests were performed in all patients, including thyroid function, lipid profile, serum lithium levels and urine drug testing.

2.3. Neuropsychological assessment

To characterize the cognitive functioning, a selected battery that included neuropsychological tasks covering the most impaired cognitive domains in BD, i.e. executive and memory functioning [3,29,32] was administered to all participants. The estimated mean intelligence quotient (IQ) of the subjects was obtained from the weighted scores of the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS-III) [33], on the basis that these two scores are highly correlated with total IQ.

The instruments administered were:

i Vocabulary, Block Design and Digits Subtests from WAIS-III [33];
ii Wisconsin Card Sorting Test (WCST) [34], to assess executive function and perseverative behaviour;
iii Stroop Color and Word Test [35], to evaluate selective attention and inhibition capacity;
iv FAS verbal fluency task of the Controlled oral Word Association Test/Categories [36], to assess executive function;
v Trail making Test (TMT), to evaluate processing speed parts A (TMT-A) and cognitive flexibility parts B (TMT-B) [37];
vi Conners' continuous Performance Test II (CPT-II) [38], to evaluate sustained attention, processing speed, and perseverative behavior;
vii The California Verbal Learning Test (CVLT) [39], to evaluate verbal learning, recall, and recognition;

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viii Rey-Osterrieth Complex figure (RCFT) [40]; to evaluate visual memory.

2.4. Biochemical measures

For each participant (patients and healthy controls), blood samples were collected between 8:00 and 9:00 to avoid variations due to the circadian rhythm. Ten millilitres of blood were withdrawn from all participants by venipuncture into a free-anticoagulant vacuum tube. Serum was separated within 2 h by centrifugation at 3500 *g* during 15 min at room temperature. All samples were stored at 80 °C until assayed in the IRBLleida Biobanc (B.0000682) and PLATAFORMA BIOBANCOS PT13/0010/0014. Afterwards, neurobiological factors were determined and all samples were assayed in duplicates. The neurobiological factors related to neurotrophins, inflammation and oxidative stress were examined as follows:

- Brain-derived neurotrophic factor (BDNF) serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Chemicon, Temecula, CA, USA), as previously described [41]. All samples were assayed in duplicates. The results were expressed as ng/ml. Intra- and inter-assay coefficients of variation were <12%.
- Serum pro-inflammatory cytokines, such as interleukin 6 (IL-6) and tumour necrosis α (TNF-α) and an anti-inflammatory cytokine, interleukin 10 (IL-10) were measured according to the procedures supplied by the manufacturer using highly sensitive sandwich-ELISA kits for TNF-α, IL-6 and IL-10 (Quantikine, R&D Systems, Minneapolis, Minn., USA). All samples were assayed in duplicates. The results were expressed as ng/ml. Intra- and inter-assay coefficients of variation were <10%.
- Oxidative damage was measured by the levels of lipid peroxidation using the thiobarbituric acid reactive substances (TBARS) method described by Wills [42]. All samples were assayed in duplicates and the results were expressed as nmol/mL.

2.5. Statistical procedure

Data analyses were carried out with the statistical package SPSS for Windows, version 22.0 (SPSS Inc., USA) and R statistical software (version 3.2.2) [43]. Demographics, clinical, and pharmacological characteristics of groups were compared with analysis of variance (ANOVAs) for continuous variables and Chi-square (or Fisher's exact test) for categorical variables as descriptive statistics analyses. All variables were assessed for normality and those variables that were not normally distributed were log-transformed. To counteract the problem of multiple comparisons, Bonferroni correction was performed on variables that displayed statistical differences between the three groups in the ANOVAs. Performance on neuropsychological tasks was compared among three groups using a multivariate analysis of variance (MANOVA), and post-hoc analyses were then performed to establish pairwise differences. Neurobiological variables were also analysed with MANOVA, and post-hoc analyses. Parametric and non-parametric correlations were carried out to explore associations between clinical, demographical and neurobiological variables to be included in further analyses. Multiple linear regression models were built to study the association between different variables (demographics and neurobiological factors) and cognitive functioning. For this purpose, neuropsychological tasks were z-transformed and grouped by cognitive domains (i.e., executive function, processing speed, inhibition, attention, and verbal and visual memories) based on our previous work [44]. A composite score was created for each cognitive domain, which included all the tests encompassed within each domain (see Table 2). The composite score was calculated as an arithmetic mean and it was used to avoid redundant information of separate tests. On measures of reaction time (low scores indicating good performance), z-scores were reversed before forming the composite score. Each cognitive composite score was then used as a dependent variable in the regression models. Multicollinearity was checked for each model using tolerance and variance inflation factor (VIF) criteria. Significant or relevant demographic variables, such as current age, premorbid IQ, BMI and neurobiological variables were included as predictive factors. The obtained results will be explained using standardized coefficient (β) and p values.

Firstly, in order to elucidate the role of clinical and neurobiological factors on cognitive functioning, Pearson's correlations were performed between these variables. Further regression models were then carried out in the sample of patients (euthymic and manic individuals) including the independent factors mentioned above together with duration of illness, number of manic and depressive episodes and number of hospitalizations.

3. Results

3.1. Demographic and clinical characteristics of the sample

Demographics, clinical features and neurobiological factors levels of the 133 participants are depicted in Table 1. Euthymic bipolar patients and healthy controls were comparable in age and gender. There were statistical differences between groups in terms of years of education, IQ, BMI, HAMD and YMRS.

With respect to pharmacological variables, most of euthymic bipolar patients (81%) were on lithium treatment (15 patients were on lithium monotherapy and 27 on combination treatment -plus antidepressant or antipsychotic-). Off the manic bipolar patients group, half of them (16 individuals) were on lithium combination treatment and the other half (16 individuals) with another mood stabilizer plus antipsychotic (i.e., valproate; see Table 1).

In terms of medical issues, there was a history of cardiovascular and endocrine issues in all groups without statistical differences ($\chi^2 = 11.8$, df = 16, p = 0.76). Particularly, they had high blood pressure (9 healthy controls, 4 euthymic and 2 manic bipolar individuals), history of diabetes mellitus type 2 (4 healthy controls, 3 euthymic and 1 manic bipolar individuals), and subclinical (4 euthymic bipolar individuals) and clinical (2 manic) hypothyroidism. Regarding body mass index (BMI), euthymic bipolar individuals were more overweight than manic individuals and healthy controls (F = 4.8; p = 0.01).

3.2. Neuropsychological performance

All neuropsychological variables included in each cognitive domain and univariate effects are listed in Table 2. As expected, in the post-hoc analyses, euthymic and manic individuals performed worse compared to healthy control group ($p < 0.0001$) in executive functioning, inhibition, processing speed, verbal and visual memory (see Fig. 1). The only domain that displayed statistical differences between euthymic and manic groups was verbal memory ($p < 0.0001$), in which euthymic patients showed better performance than manic patients, but worse than healthy controls.

3.3. Descriptive analyses of neurobiological factors and associations with demographic, clinical and pharmacological variables

BDNF levels in both groups of bipolar patients (euthymic and manic individuals; p = 0.039 and $p < 0.0001$ respectively) were

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Table 1
Demographical, clinical and neurobiological variables for euthymic bipolar and manic patients and healthy controls.

Variables	Healthy Controls (n=49)	Euthymic Bipolar Patients (n=52)	Manic patients (n=32)	F or χ^2/p	Bonferroni post-Hoc
Age, y	48.3 (12.1)	47.52 (11.9)	41.25 (12.9)	3.6/0.029	HC>Ma
Gender, (number of males, %)	21 (42.9)	26 (50)	18 (56.3)	1.43/NS	
Mean estimated premorbid IQ	115.3 (9.9)	102.6 (11.6)	97.8 (11.6)	28.6/<0.0001	HC>Eu; HC>Ma
Current work status, N (%)					
Active	40 (81.6)	21 (40.4)	13 (40.6)	28/*	
Inactive	2 (4.1)	7 (13.5)	10 (31.3)		
Retired/Disabled	7 (14.3)	24 (46.2)	9 (28.1)		
Positive family history of mental illness, N (%)	18 (36.7)	39 (75)	15 (46.9)	15.8/*	
Education, y	12.7 (2.9)	10.3 (2.7)	11.75 (3.4)	7.9/0.001	HC>Eu
GAF score	NA	73 (9.5)	31.41 (7.1)	545.8/*	
BMI, kg/m^2	26.5 (5)	29 (4.6)	26.5 (3.8)	0.010	Eu>HC; Eu>Ma
Clinical Variables					
YMRS score	0.6 (1.1)	1.4 (1.7)	31.3 (5.9)	1118.2/*	Ma>Eu; Ma>HC
HAM-D score	0.9 (1.4)	2.4 (2.3)	8.3 (3.7)	100/*	Ma>Eu>HC;
Age of onset, y	NA	24.5 (10.3)	29.3 (10.7)	4.2/0.043	Ma>HC
No. of hospitalizations	NA	2.7 (2.7)	3 (2.6)	0.3/NS	
Duration of illness, y	NA	22.9 (12.4)	11.9 (11.2)	16.8/*	
Total no. of manic episodes	NA	2.6 (2.7)	2.9 (3.7)	0.2/NS	
Years of stabilization	NA	6 (5.9)	3 (3.4)	6.8/0.011	
Lifetime history of psychotic symptoms, N (%)	NA	41 (78.8)	27 (84.4)	0.39/NS	
Lifetime history of seasonal pattern, N (%)	NA	29 (55.8)	18 (56.3)	0.002/NS	
Personal history of suicide attempts, N (%)	NA	20 (38.5)	6 (18.8)	3.6/0.06	
Diagnosis, N (%)					
Bipolar I disorder	NA	34 (65.4)	31 (96.9)	11.1/0.001	
Bipolar II disorder	NA	18 (34.6)	1 (3.1)		
Type of current medication, N (%)					
Lithium monotherapy	NA	15 (28.8)	0	18.8/*	
Lithium + combination	NA	27 (51.9)	16 (50)		
Valproate + combinarion	NA	8 (15.4)	16 (50)		
None	NA	2 (3.8)	0		
Lithium					
Years of treatment, y	NA	9.2 (6.7)	1.2 (1.6)	21.6/*	
Serum lithium levels, mml/dL	NA	0.7 (0.2)	0.65 (0.1)	0.7/NS	
Lithium dosage, mg/day	NA	1128.6 (278.7)	1062.5 (215.6)	0.7/NS	
Biomarkers					
BDNF, ng/ml	45.86 (13.6)	40 (9.9)	35.05 (10.6)	8.6/*	HC>Eu; HC>Ma
logIL-6	0.86 (0.5)	1.09 (0.6)	1.23 (0.7)	4.1/0.018	Ma>HC
logIL-10	−2.24 (0.4)	−1.18 (1.4)	−1.18 (1.4)	12.5/*	Ma>HC; Eu>HC
logTNF	−0.51 (2.4)	−0.04 (2.8)	0.71 (2.8)	2/0.14	
logTBARS	2.51 (0.6)	3.08 (1)	2.79 (0.9)	5.6/0.005	Eu>HC

Values represent mean (SD) unless otherwise specified
Statistics of between-subject effects from the multivariate analyses of variance. Abbreviations: GAF = Global Assessment of Functioning, YMRS = Young Mania Rating Scale, HAM-D = Hamilton Rating Scale for Depression, NA = Not applicable, NS = Not significant. HC=Healthy Controls, Eu=Euthymic Patients, Ma=Manic patients. *=<0.0001.

significantly lower compared to healthy controls. Conversely, the pro-inflammatory cytokine interleukin 6 (IL-6) levels were significantly higher in the group of manic patients compared to healthy controls ($p = 0.019$), and the anti-inflammatory interleukin 10 (IL-10) levels were higher in both groups of patients compared to healthy controls (both comparisons with statistical significance; $p < 0.0001$). Levels of TBARS were higher in euthymic bipolar group compared to healthy controls ($p = 0.003$); but there were not statistical differences between manic patients group and the other groups.

Correlations between neurobiological factors and demographic variables showed that there was an association between IL-6 and BMI ($r = 0.515$; $p < 0.0001$) and with current age ($r = 0.313$; $p < 0.0001$) in all participants. Premorbid IQ displayed a significant relationship with IL-10 (r=0.268; $p = 0.002$) and with levels of oxidative damage (TBARS; r=0.247; $p = 0.005$).

BDNF showed a negative correlation with HDRS (r=0.251, $p = 0.004$) and YMRS (r=0.284, $p = 0.001$) in all participants. Conversely, as it was expected, IL-6 displayed a positive association with the same scales (HDRS: $r = 0.176$, $p = 0.045$; and YMRS: $r = 0.192$, $p = 0.029$). IL-10 did not show any association with these scales. When analysing patients alone (euthymic and manic), correlations between clinical variables and neurobiological factors showed that only IL-6 was associated with duration of illness ($r = 0.245$; $p = 0.025$).

Regarding pharmacological treatment, most bipolar euthymic patients and half of the manic patients were on lithium treatment. There was not any association between lithium and neurobiological factors levels, with the exceptions of IL-6, which correlated positively with lithium levels ($r = 0.33$; $p = 0.011$); and T-BARS, where patients who were on lithium combination treatment displayed higher levels ($F = 4.7$; $p = 0.035$) compared to patients who were on lithium monotherapy.

Bipolar type I and type II euthymic individuals did not display any statistical differences in neurobiological factors levels (data not shown).

3.4. Association of neurobiological factors, demographics and BMI with cognitive functioning

Six regression models were performed, one for each neuropsychological domain in order to explore the association of neurobiological factors and other demographic variables with cognitive functioning (see Table 3). Only the models of executive functioning and verbal memory were significant, with a $R^2 = 0.56$ and 0.58, respectively. In particular, BDNF ($\beta = 0.01$, $p = 0.02$) was the only neurobiological factor that explained executive functioning together with other variables: being manic (β=0.4, $p = 0.012$), current age (β=0.023, $p < 0.0001$) and premorbid IQ ($\beta = 0.03$,

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Table 2
Neuropsychological Test Results: Comparison of Euthymic Bipolar and Manic Patients and Healthy Controls.

Neurocognitive Tests	Healthy Controls (N = 49)[a]	Euthymic Bipolar Patients (N = 52)	Manic Patients (N=32)	F/p	Bonferroni Post Hoc
Executive Functioning Domain				<0.0001	HC>Eu; HC>Ma
TMT part B	62.1 (26)	117 (72.2)	117.9 (64.3)	13/<0.0001	HC>Eu; HC>Ma
FAS	43.47 (9.2)	34.25 (11.6)	37.16 (11.9)	8.8/<0.0001	HC>Eu; HC>Ma
WAIS-III digit span backward	6.51 (1.8)	5.06 (2)	4.31 (1.6)	14.8/<0.0001	HC>Eu; HC>Ma
Number of categories WCST	4.16 (2)	3.13 (2)	1.94 (1.5)	12.4/<0.0001	HC>Eu >Ma; HC>Ma
Inhibition Domain				<0.0001	HC>Eu; HC>Ma
Stroop inhibition	45.87 (9.6)	34.94 (11.9)	30.47 (11.4)	38.5/<0.0001	HC>Eu; HC>Ma
No. of perseverative errors WCST	10.6 (9.5)	16.81 (12.7)	10.87 (6.5)	5.4/0.006	HC>Eu; Ma>Eu
No. of perseverative errors CPT	0.24 (0.6)	2.42 (4.3)	3.35 (3.6)	9.1/<0.0001	HC>Eu; HC>Ma
Attention Domain				0.002	HC>Eu
Stroop interference	4.92 (7.7)	2.63 (10.7)	−0.4 (8.9)	3.1/0.05	HC>Ma
WAIS-III digit span forward	8.76 (1.9)	8.06 (2.1)	8.34 (1.6)	1.6/0.21	NS
CPT-II detectability	1.02 (0.4)	0.72 (0.4)	0.7 (0.5)	7.3/0.001	HC>Eu; HC>Ma
Processing Speed Domain				<0.0001	HC>Eu; HC>Ma
TMT part A	32.4 (12.5)	54 (30.4)	50.19 (19.9)	11.5/<0.0001	HC>Eu; HC>Ma
CPT-II hit reaction time	428.43 (63.3)	479.18 (98.4)	501.65 (103.2)	6.9/0.001	HC>Eu; HC>Ma
Verbal Memory				<0.0001	HC>Eu >Ma; HC>Ma
CVLT first trial	7.07 (2.1)	5.9 (2)	4.94 (1.6)	11.4/<0.0001	HC>Eu; HC>Ma
CVLT total words	58.93 (7.5)	48.13 (12.1)	40.34 (10.6)	31.9/<0.0001	HC>Eu >Ma; HC>Ma
CVLT immediate recall	13.93 (2)	10.12 (3.7)	7.06 (3.5)	45.7/<0.0001	HC>Eu >Ma; HC>Ma
CVLT delayed recall	14.56 (1.6)	11.19 (3.1)	7.28 (3.6)	51.3/<0.0001	HC>Eu >Ma; HC>Ma
CVLT recognition	15.82 (0.4)	14.62 (1.7)	14.03 (2.6)	11.2/<0.0001	HC>Eu; HC>Ma
Visual Memory				<0.0001	HC>Eu; HC>Ma
RCFT immediate recall	25.22 (4.9)	18.2 (6.5)	16 (7.4)	23.8/<0.0001	HC>Eu; HC>Ma
RCFT delayed recall	25.26 (5.5)	19.26 (7.3)	15.22 (7.9)	20.7/<0.0001	HC>Eu >Ma; HC>Ma

[a]Values shown as mean (SD).
Statistics of between-subject effects from the multivariate analyses of variance.
Abbreviations: CVLT = California Verbal Learning Test, TMT = Trail Making Test, RCFT=Rey Complex Figure Test, HC=Healthy Controls, Eu=Euthymic Patients, Ma=Manic patients.

$p < 0.0001$), and explained a 56% of variance ($F = 16.5$; $df = 9115$; $p < 0.0001$) (see Fig. 2). Again BDNF ($\beta = 0.013$, $p = 0.005$) together with BMI (β=-0.4, $p = 0.005$) and other variables [being euthymic (β=0.345, $p = 0.019$), being manic (β=1.07, $p < 0.0001$), current age (β=-0.015, $p = 0.002$) and premorbid IQ ($\beta = 0.018$, $p < 0.0001$)] predicted worse performance in verbal memory, and explained a 58% of variance ($F = 17.2$; $df = 9.115$; $p < 0.0001$) (see Fig. 2). The rest of neurobiological factors did not predict any other cognitive domain, although the models were significant.

3.5. Association of neurobiological factors and clinical variables with cognitive functioning in Bipolar Patients

Again six regression models were performed only analysing euthymic and manic bipolar individuals (see Table 4). Current age and premorbid IQ were predictor factors in all models ($p < 0.05$). Being a manic bipolar individual was associated with worse performance in executive functioning (β=0.33, $p = 0.029$), verbal memory (β=0.864, $p < 0.0001$) and visual memory (β=0.459, $p = 0.039$).

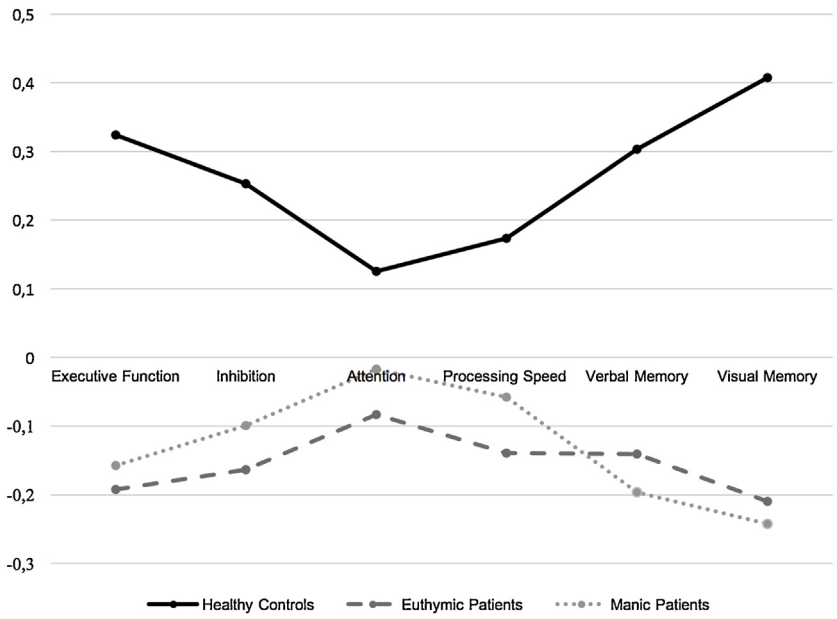

Fig. 1. Neuropsychological performance adjusted by age, premorbid IQ and years of education from all participants.

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Table 3
Multiple regression models of the association between neurobiological factors and cognition in bipolar disorder individuals (euthymic an manic) and healthy controls. The values correspond to all factors included in the models. Please note that only Executive Functioning and Verbal Memory models were the only that neurobiological factors were significant.

Cognitive Domain	Predictor	β	Standard error β	Standardized β	p
Executive Functioning	Euthymic	−0.221	0.130	−0.145	0.092
	Maniac	−0.403	0.158	−0.232	0.012
	Current age	−0.023	0.004	−0.395	<0.0001
	Premorbid IQ	0.030	0.004	0.532	<0.0001
	BDNF	0.010	0.004	0.155	0.020
	logIL6	0.022	0.098	0.017	0.826
	logTNF	0.001	0.018	0.005	0.939
	logTBARS	−0.029	0.057	−0.034	0.610
	BMI	−0.014	0.012	−0.087	0.259
Inhibition	Euthymic	−0.389	0.154	−0.251	0.013
	Maniac	−0.422	0.188	−0.238	0.026
	Current age	−0.023	0.005	−0.378	0.000
	Premorbid IQ	0.022	0.005	0.387	0.000
	BDNF	0.004	0.005	0.059	0.445
	logIL6	−0.018	0.117	−0.014	0.878
	logTNF	−0.023	0.021	−0.081	0.271
	logTBARS	0.083	0.067	0.096	0.215
	BMI	−0.010	0.014	−0.063	0.486
Attention	Euthymic	−0.185	0.136	−0.153	0.177
	Maniac	−0.009	0.166	−0.007	0.956
	Current age	−0.011	0.004	−0.241	0.011
	Premorbid IQ	0.011	0.005	0.248	0.017
	BDNF	0.007	0.004	0.152	0.085
	logIL6	0.024	0.103	0.024	0.817
	logTNF	0.020	0.019	0.092	0.272
	logTBARS	−0.089	0.059	−0.132	0.135
	BMI	−0.004	0.013	−0.033	0.745
Processing speed	Euthymic	−0.554	0.162	−0.324	0.001
	Maniac	−0.781	0.197	−0.400	<0.0001
	Current age	−0.036	0.005	−0.542	<0.0001
	Premorbid IQ	0.016	0.005	0.244	0.005
	BDNF	0.003	0.005	0.039	0.591
	logIL6	0.038	0.123	0.026	0.759
	logTNF	0.001	0.022	0.003	0.967
	logTBARS	0.076	0.070	0.079	0.283
	BMI	−0.008	0.015	−0.045	0.603
Verbal Memory	Euthymic	−0.345	0.145	−0.199	0.019
	Maniac	−1.071	0.177	−0.543	<0.0001
	Current age	−0.015	0.005	−0.224	0.002
	Premorbid IQ	0.018	0.005	0.279	<0.0001
	BDNF	0.013	0.005	0.185	0.005
	logIL6	0.053	0.110	0.037	0.628
	logTNF	0.005	0.020	0.015	0.813
	logTBARS	−0.088	0.063	−0.091	0.166
	BMI	−0.040	0.014	−0.219	0.005
Visual Memory	Euthymic	−0.325	0.172	−0.163	0.061
	Maniac	−0.742	0.209	−0.327	0.001
	Current age	−0.026	0.006	−0.331	<0.0001
	Premorbid IQ	0.032	0.006	0.432	<0.0001
	BDNF	<0.0001	0.005	0.006	0.931
	logIL6	−0.150	0.130	−0.090	0.252
	logTNF	−0.046	0.024	−0.125	0.054
	logTBARS	−0.113	0.075	−0.101	0.134
	BMI	−0.010	0.016	−0.046	0.556

Abbreviations: IQ: intelligence quotient; BMI: body mass index.

Of the clinical variables, the number of manic episodes (β=-0.066, p = 0.011) was the only clinical variable that was associated with worse performance on the attention domain, together with current age (β=0.025, p = 0.001) and premorbid IQ (β = 0.014, p = 0.015), and explained a 32% of variance (F = 2.7; df = 12, 70; p = 0.004). The rest of clinical variables were not associated with any of the other domains.

Verbal memory was associated with BDNF levels (β = 0.023, p = 0.001), BMI (β=0.05, p = 0.017), together with being manic (β=0.864, p < 0.0001), current age (β=0.018, p = 0.023) and premorbid IQ (β = 0.022, p = 0.001), and explained a 54% of variance (F = 7; df = 12, 70; p < 0.0001).

4. Discussion

The most remarkable finding of this study was the significant association of neurotrophins with illness phases and their significant impact on cognitive dysfunction in bipolar individuals,

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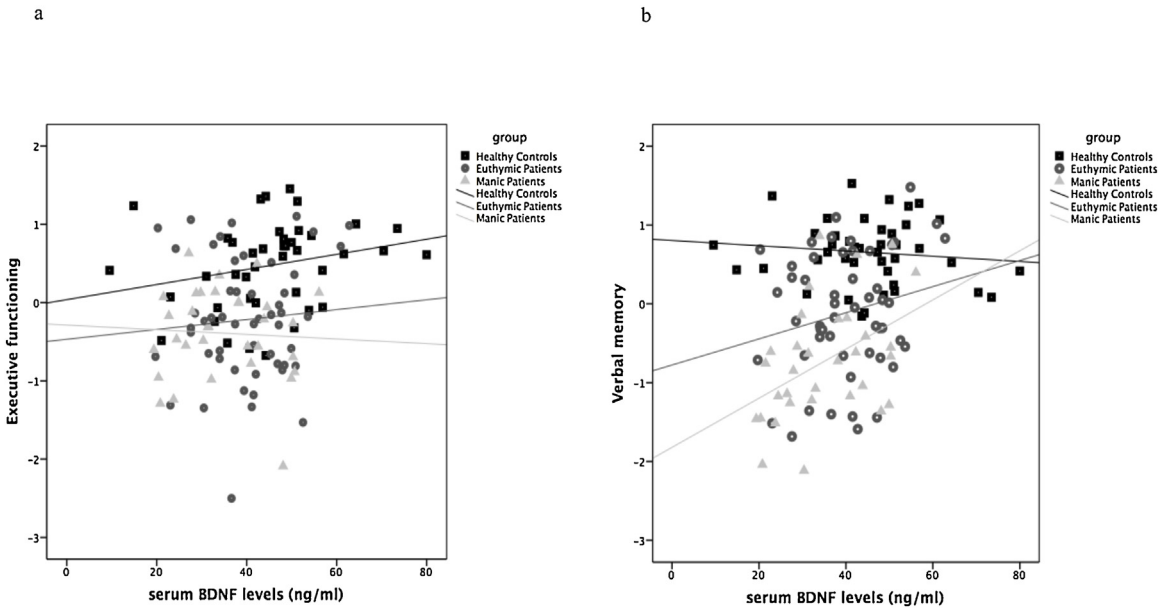

Fig. 2. Scatter plots displaying predicted executive functioning (a) and verbal memory (b) by BDNF levels clustered by euthymic and manic bipolar individuals and healthy controls.

affecting particularly executive functioning and verbal memory. This represents valuable information as few studies have explored the role of neurobiological factors on cognitive symptoms in BD, and results had been contradictory.

Linking neurobiological factors and cognition, our results are partially consistent with the few previous studies that focus on BNDF and cognitive outcome in BD, specifically in executive functioning [45] and verbal memory [46,47]. In the same line, TNF-α, was found to be negatively correlated with accuracy on the delayed memory component on the Rey Auditory Verbal Learning Test (RAVLT) in euthymic type I individuals [48]. Remarkably, the presence of verbal memory impairment across mood phases may indicate that these deficits are trait markers of bipolar illness [49].

Furthermore, current evidence indicates that the BD phenotype is heterogeneous and there may be different illness trajectories that could at least in part be explained by distinct underlying pathophysiology [50,51]. The current study provides evidence that other conditions such as obesity can play a role in defining verbal memory as a trait marker, as has been observed in previous studies [52–54]. In a recent study from our group, the interaction of bipolar disorder and obesity was found to impact cognitive dysfunction at a single point in time and long-term [14].

Strikingly, the relation between BDNF and verbal memory found in our study has not been replicated in healthy population in a recent study [55]. There are also previous data showing a positive [56], a negative [57] or no correlation [58] between serum BDNF and memory functions in healthy subjects. All these conflicting results could be explained by the fact that the relationship between cognition and BDNF may be affected by many other factors such as mood state, sociodemographic and lifestyle factors (for example: physical exercise, BMI and others) [55]. In the same line, BDNF Val66Met genotype has been described as a potential risk factor for obesity and insulin resistance measures in patients with BD who are also receiving antipsychotic medication [59].

Regarding the association between clinical variables and neurobiological factors, duration of illness was the only clinical variable related with an inflammatory marker (IL-6) in the current study. In the same line, another study found that IL-6 levels showed significant differences between early and late stages of BD [60]. Consistent with our results, in a recent meta-analysis [21], duration of illness in euthymia was not associated with BDNF levels, suggesting that it may not be a useful marker of illness stage but it could be a marker of illness activity instead. Furthermore, it has been reported that BDNF levels did not differ between bipolar patients, unaffected first-degree relatives and healthy controls. Thus, BDNF levels may not reflect high genetic risk for BD, acting as state marker rather than trait marker for the disease [61]. The correlation of BDNF levels with mood psychometric scales and mood phases may corroborate this hypothesis.

In terms of the association between psychopharmacological treatment and neurobiological factors, in our study lithium variables were not significantly associated with BDNF levels which may indicate that lithium did not influence the relationship between neurotrophins and cognition. In this paper the impact of psychopharmacological treatment on the association between neurobiological factors and cognitive dysfunction was not directly assessed because it was not methodologically designed for this purpose. Focusing on lithium, it has been reported in the current literature that excellent lithium responders (ELR) had higher plasma BDNF levels and performed better on all neuropsychological tests than the remaining lithium patients [62] but worse than healthy controls in the long-term [63]. Treatment with mood stabilizers (i.e. lithium) was associated with lower levels of DNA methylation of BDNF promoter [64]. Further analyses of neurobiological factors by selecting individuals taking lithium are warranted to understand the effects of lithium on cognition.

In our study, neither inflammatory nor oxidative stress markers were associated with cognitive performance, which differ from previous studies [10,48,65]. Of note, many other difficult-to-control factors related with mood symptoms which may result in inflammation and oxidative stress, were not assessed such as: undiagnosed inflammatory medical comorbidities, history of early childhood adversity [66], dysfunctional gut-microbiota, dietary patterns, and low-grade idiopathic systemic inflammation [67–72].

The reported discrepancies could arguably be attributed to some methodological limitations of the current study that warrant acknowledgement: the variety of techniques to measure neurobiological factors, demographics and clinical characteristics of the sample, such as age and gender-related brain characteristics [73], BD subtype [74] and medication history [75]. Although the sample

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Table 4
Multiple regression models of the association between neurobiological factors and cognition in bipolar disorder individuals (euthymic and manic). The values correspond to all factors included in the models. Please note that only Verbal Memory model was the only that neurobiological factors were significant.

Cognitive Domain	Predictor	β	Standard error β	Standardized β	p
Executive Functioning	Maniac	−0.333	0.148	−0.226	0.028
	Current age	−0.032	0.006	−0.565	<0.0001
	Premorbid IQ	0.037	0.005	0.608	<0.0001
	BDNF	0.003	0.005	0.047	0.555
	logIL6	0.085	0.119	0.069	0.480
	logTNF	0.011	0.020	0.044	0.584
	logTBARS	−0.080	0.060	−0.107	0.184
	BMI	−0.016	0.017	−0.100	0.334
	Age at onset	0.004	0.006	0.055	0.552
	Number of manic episodes	−0.042	0.022	−0.182	0.063
	Number of depressive episodes	0.024	0.027	0.086	0.367
Inhibition	Maniac	−0.205	0.205	−0.125	0.321
	Current age	−0.038	0.008	−0.594	<0.0001
	Premorbid IQ	0.023	0.007	0.341	0.001
	BDNF	0.010	0.007	0.130	0.187
	logIL6	0.023	0.165	0.017	0.890
	logTNF	−0.025	0.028	−0.087	0.382
	logTBARS	0.111	0.083	0.133	0.184
	BMI	−0.019	0.023	−0.107	0.405
	Age at onset	0.015	0.009	0.201	0.085
	Number of manic episodes	−0.052	0.031	−0.200	0.101
	Number of depressive episodes	0.065	0.037	0.207	0.084
Attention	Maniac	0.179	0.169	0.138	0.294
	Current age	−0.016	0.007	−0.322	0.019
	Premorbid IQ	0.014	0.006	0.264	0.016
	BDNF	0.003	0.006	0.055	0.590
	logIL6	0.040	0.136	0.038	0.769
	logTNF	0.035	0.023	0.155	0.139
	logTBARS	−0.091	0.068	−0.140	0.184
	BMI	0.011	0.019	0.08	0.550
	Age at onset	−0.009	0.007	−0.150	0.217
	Number of manic episodes	−0.065	0.026	−0.323	0.013
	Number of depressive episodes	0.020	0.031	0.08	0.522
Processing speed	Maniac	−0.323	0.221	−0.178	0.148
	Current age	−0.048	0.009	−0.689	<0.0001
	Premorbid IQ	0.022	0.007	0.297	0.004
	BDNF	0.005	0.008	0.057	0.552
	logIL6	0.086	0.178	0.057	0.630
	logTNF	0.009	0.030	0.028	0.770
	logTBARS	0.050	0.089	0.054	0.579
	BMI	−0.018	0.025	−0.088	0.481
	Age at onset	0.010	0.009	0.117	0.299
	Number of manic episodes	0.006	0.033	0.020	0.865
	Number of depressive episodes	−0.011	0.040	−0.032	0.781
Verbal Memory	Maniac	−0.863	0.181	−0.509	<0.0001
	Current age	−0.018	0.007	−0.283	0.012
	Premorbid IQ	0.022	0.006	0.309	0.001
	BDNF	0.023	0.007	0.287	0.001
	logIL6	0.084	0.146	0.060	0.568
	logTNF	0.028	0.025	0.096	0.258
	logTBARS	−0.115	0.073	−0.134	0.120
	BMI	−0.050	0.020	−0.267	0.017
	Age at onset	−0.0000499	0.008	−0.001	0.995
	Number of manic episodes	−0.017	0.027	−0.065	0.533
	Number of depressive episodes	−0.007	0.033	−0.022	0.830
Visual Memory	Maniac	−0.455	0.217	−0.234	0.040
	Current age	−0.031	0.009	−0.417	0.001
	Premorbid IQ	0.036	0.007	0.444	<0.0001
	BDNF	0.005	0.008	0.050	0.571
	logIL6	−0.114	0.175	−0.071	0.515
	logTNF	−0.054	0.030	−0.159	0.076
	logTBARS	−0.123	0.088	−0.125	0.165
	BMI	−0.012	0.024	−0.057	0.622
	Age at onset	−0.001	0.009	−0.012	0.911
	Number of manic episodes	−0.024	0.033	−0.079	0.467
	Number of depressive episodes	−0.046	0.040	−0.124	0.245

Abbreviations: IQ: intelligence quotient; BMI: body mass index.

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size of the present study is acceptable given the type of population, the study should be seen as exploratory given the number of statistical analyses conducted. In any case, these analyses served to cover different aspects of the intricate variables involved in cognitive performance of bipolar patients. In our sample euthymic bipolar disorder individuals might represent mid-late stage of the illness with low rates of recurrence which might not be representative of the majority of bipolar patients, being biased to patients with better outcomes [76]. But including manic patients groups in the sample has allowed us to demonstrate the cognitive consequences of neurotrophins in different mood phases. Moreover, our sample was balanced in terms of gender and there were no statistical differences between groups according to BD type I and type II in terms of neurobiological factors levels. The cross-sectional nature of the study and the methodological limitations described above preclude the establishment of more conclusive evidence about the neuroprogression or neurodevelopmental nature of the illness or about the causality and direction of the associations. But the correlation findings shed light on this intriguing field. Some authors state that there may be a subgroup of patients not exceeding 25–40% that could show phenomena of cycle acceleration [77]. Moreover, there is growing evidence that about one third of euthymic BD patients have more severe cognitive deficits than usually reported in the literature, while a similar proportion are indistinguishable from healthy controls in terms of cognitive functioning [78]. Clinical evidence supporting the concept of neuroprogression in BD is scarce and limited [79], but the longitudinal studies that have been published to date are too small and too short-term to prove that there is no progression [80]. This controversy is currently still under debate [7]. Future investigation using larger samples, drug-naïve patients, longitudinal designs incorporating repeated measures of these markers [81], selecting homogenous treatment response like excellent lithium responders and assessing the impact of childhood trauma [66] and lifestyle factors (for example: physical exercise and BMI) [55] are needed to reveal the specific connections between BD, neurobiological factors and neurocognitive performance. A careful attention to attrition in those cohorts will be critical.

4.1. Conclusion

In conclusion, our findings support the hypothesis that neurotrophic mechanisms correlate with clinical variables and cognitive functioning, specifically in executive functioning and verbal memory. Other variables such as mood state and obesity may underlie the link between neurotrophins and cognition. Additional work is needed to understand how pro-inflammatory and oxidative damage processes affect brain function and induce cognitive impairment [10]. Monitoring neurobiological factors levels at the time of assessment in clinical psychiatry could help to tailor specific and individualized treatment interventions not only to treat mood symptoms but also to revert biological changes associated with the illness [16] such as cognitive and functional decline.

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Conflict of interest

E.V. has received research grants and served as consultant, advisor or speaker for the following companies: AB-Biotics, Almirall, Allergan, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Elan, Eli Lilly, Ferrer, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer Inc., Roche, Sanofi-Aventis, Servier, Solvay, Schering-Plough, Shire, Sunovion, Takeda, United Biosource Corporation, and Wyeth. E.V. has received research funding from the Spanish Ministry of Science and Innovation, the Stanley Medical Research Institute and the 7th Framework Programme of the European Union. The rest of the authors have no conflicts of interest to declare.

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References

[1] Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 2011;68:241–51, doi:http://dx.doi.org/10.1001/archgenpsychiatry.2011.12.
[2] Bourne C, Aydemir Ö, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JTO, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr Scand 2013;128:149–62, doi:http://dx.doi.org/10.1111/acps.12133.
[3] Mora E, Portella MJ, Forcada I, Vieta E, Mur M. Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. Psychol Med 2013;25:1–10, doi:http://dx.doi.org/10.1017/S0033291712001948.
[4] Samamé C, Martino DJ, Strejilevich Sa. Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. J Affect Disord 2014;164:130–8, doi:http://dx.doi.org/10.1016/j.jad.2014.04.028.
[5] Cardoso T, Bauer IE, Meyer TD, Kapczinski F, Soares JC. Neuroprogression and cognitive functioning in bipolar disorder: a systematic review. , doi:http://dx.doi.org/10.1007/s11920-015-0605-x.
[6] Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet 2016;387:1561–72, doi:http://dx.doi.org/10.1016/S0140-6736(15)00241-X.
[7] Vieta E, Salagre E, Grande I, Carvalho AF, Fernandes BS, Berk M, et al. Early intervention in bipolar disorder. Am J Psychiatry 2018, doi:http://dx.doi.org/10.1176/appi.ajp.2017.17090972 appiajp201717090972.
[8] Tse S, Chan S, Ng KL, Yatham LN. Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder. Bipolar Disord 2014;16:217–29, doi:http://dx.doi.org/10.1111/bdi.12148.
[9] Millan MJ, Agid Y, Brüne M, Bullmore ET, Carter CS, Clayton NS, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov 2012;11:141–68, doi:http://dx.doi.org/10.1038/nrd3628.
[10] Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC. Inflammatory mediators of cognitive impairment in bipolar disorder. J Psychiatr Res 2014;56:18–27, doi:http://dx.doi.org/10.1016/j.jpsychires.2014.04.017.
[11] McIntyre R, Woldeyohannes H, Soczynska JK, Miranda A, Lachowski A, Liauw SS, et al. The rate of metabolic syndrome in euthymic Canadian individuals with bipolar I/II disorder. Adv Ther 2010;27:828–36.

[12] Calkin CV, Alda M. Insulin resistance in bipolar disorder: relevance to routine clinical care. Bipolar Disord 2015;17:683–8, doi:http://dx.doi.org/10.1111/bdi.12330.
[13] Strejilevich Sa, Samamé C, Martino DJ. The trajectory of neuropsychological dysfunctions in bipolar disorders: a critical examination of a hypothesis. J Affect Disord 2015;175C:396–402, doi:http://dx.doi.org/10.1016/j.jad.2015.01.018.
[14] Mora E, Portella MJ, Martinez-Alonso M, Teres M, Forcada I, Vieta E, et al. The impact of obesity on cognitive functioning in euthymic bipolar patients. J Clin Psychiatry 2017;78:e924–32, doi:http://dx.doi.org/10.4088/JCP.16m10968.
[15] García-Bueno B, Caso JR, Leza JC. Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. Neurosci Biobehav Rev 2008;32:1136–51, doi:http://dx.doi.org/10.1016/j.neubiorev.2008.04.001.
[16] Pfaffenseller B, Fries GR, Wollenhaupt-Aguiar B, Colpo GD, Stertz L, Panizzutti B, et al. Neurotrophins, inflammation and oxidative stress as illness activity biomarkers in bipolar disorder. Expert Rev Neurother 2013;13:827–42, doi:http://dx.doi.org/10.1586/14737175.2013.811981.
[17] Fernandes BS, Berk M, Turck CW, Steiner J, Gonçalves C-A. Decreased peripheral brain-derived neurotrophic factor levels are a biomarker of disease activity in major psychiatric disorders: a comparative meta-analysis. Mol Psychiatry 2014;19:750–1, doi:http://dx.doi.org/10.1038/mp.2013.172.
[18] Mansur RB, Cunha GR, Asevedo E, Zugman A, Levandowski L, Gadelha A, et al. Socioeconomic disadvantage moderates the association between peripheral biomarkers and childhood psychopathology. PLoS One 2016;6:1–14, doi:http://dx.doi.org/10.1371/journal.pone.0160455.
[19] Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol Psychiatry 2013;74:15–25, doi:http://dx.doi.org/10.1016/j.biopsych.2013.01.007.
[20] Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res 2014;218:61–8, doi:http://dx.doi.org/10.1016/j.psychres.2014.04.005.
[21] Fernandes BS, Molendijk ML, Köhler CA, Soares JC, CMGS Leite, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder : a meta-analysis of 52 studies. BMC Med 2015;1–22, doi:http://dx.doi.org/10.1186/s12916-015-0529-7.
[22] Rosa AR, Singh N, Whitaker E, De Brito M, Lewis AM, et al. Altered plasma glutathione levels in bipolar disorder indicates higher oxidative stress ; a possible risk factor for illness onset despite normal brain-derived neurotrophic factor (BDNF) levels Altered plasma glutathione levels in bipolar disorder indic. Psychol Med 2014;44:2409–18, doi:http://dx.doi.org/10.1017/S0033291714000014.
[23] Rosenblat JD, Brietzke E, Mansur RB, Maruschak NA, Lee Y, McIntyre RS. Inflammation as a neurobiological substrate of cognitive impairment in bipolar disorder: evidence, pathophysiology and treatment implications. J Affect Disord 2015;188:149–59, doi:http://dx.doi.org/10.1016/j.jad.2015.08.058.
[24] Barbosa IG, Bauer ME, Machado-Vieira R, Teixeira AL. Cytokines in bipolar disorder: paving the way for neuroprogression. Neural Plast 2014;2014:360481, doi:http://dx.doi.org/10.1155/2014/360481.
[25] Rosenblat JD, McIntyre RS. Bipolar disorder and inflammation. Psychiatr Clin North Am 2016;39:125–37, doi:http://dx.doi.org/10.1016/j.psc.2015.09.006.
[26] First M, Spitzer R, Gibbon M, Structured AlE. Clinical interview for DSM-IV Axis I disorders (SCID-I), clinician version, user's guide. Barcelona, Spain: Masson; 1999.
[27] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[28] Young R, Biggs J, Ziegler V, DA M. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–35.
[29] Mur, Portella MJ, Martínez-Arán A, Pifarré J, Vieta E. Persistent neuropsychological deficit in euthymic bipolar patients: executive function as a core deficit. J Clin Psychiatry 2007;68:1078–86.
[30] Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, 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;11:453–73, doi:http://dx.doi.org/10.1111/j.1399-5618.2009.00726.x.
[31] National Heart LaBI NI of D and D and KD. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults. Bethesda, Md. 1998.
[32] Martinez-Aran A, Torrent C, Tabares-Seisdedos R, Salamero M, Daban C, et al. Neurocognitive impairment in bipolar patients with and without history of psychosis. J Clin Psychiatry 2008;69:233–9.
[33] Wechsler D. Wechsler adult intelligence Scale-III technical manual (Spanish version). Madrid: TEA; 2001.
[34] Heaton R. The wisconsin card sorting test manual. Odessa, TX: Psychologi; 1981.
[35] Golden C, Stroop Color. Word test. Chicago, IL: Stoelting; 1978.
[36] Benton A, Hamsher K. Multilingual aphasia examination. The univer. Iowa City, IA. 1976.
[37] Reitan R. Validity of the Trail making Test as an indicator of organic brain damage. Percept Mot Skills 1958;8:271–6.
[38] Conners C. Conners' continuous performance test II manual. Toronto: Multi-Heal; 2000.
[39] Delis D. The California verbal learning test manual. New York, NY: Psychologi; 1987.
[40] Meyers J, Meyers K. Rey complex figure test and recognition trial. Odessa, FL: Psychologi; 1995.
[41] Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. Late-stage bipolar disorder. Int J Neuropsychopharmacol 2009;12:447–58, doi:http://dx.doi.org/10.1017/S1461145708009310.
[42] Wills ED. Mechanisms of lipid peroxide formation in animal tissues. Biochem J 1966;99:667–76.
[43] R Core Team. R: a language and environment for statistical computing. 2015.
[44] Mur M, Portella MJ, Martínez-Arán A, Pifarré J, Vieta E. Long-term stability of cognitive impairment in bipolar disorder: a 2-year follow-up study of lithium-treated euthymic bipolar patients. J Clin Psychiatry 2008;69:712–9.
[45] Lee S, Wang T, Chen S, Chang Y, Chen P. The correlation between plasma brain-derived neurotrophic factor and cognitive function in bipolar disorder is modulated by the BDNF Val66Met polymorphism. Nat Publ Gr 2016;1–8, doi:http://dx.doi.org/10.1038/srep37950.
[46] Dias V, Brissos S, Frey B, Andreazza AC, Cardoso C, Kapczinski F. Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder. Bipolar Disord 2009;11:663–71.
[47] Cao B, Bauer IE, Sharma AN, Mwangi B, Frazier T, Lavagnino L, et al. Reduced hippocampus volume and memory performance in bipolar disorder patients carrying the BDNF val66met met allele. J Affect Disord 2016;198:198–205, doi:http://dx.doi.org/10.1016/j.jad.2016.03.044.
[48] Doganavsargil-Baysal O, Cinemre B, Aksoy UM, Akbas H, Metin O, Fettahoglu C, et al. Levels of TNF-??, soluble TNF receptors (sTNFR1, sTNFR2), and cognition in bipolar disorder. Hum Psychopharmacol 2013;28:160–7, doi:http://dx.doi.org/10.1002/hup.2301.
[49] Gualtieri CT, Johnson LG. Comparative neurocognitive effects of 5 psychotropic anticonvulsants and lithium. MedGenMed 2006;8:46 doi:541762 [pii]..
[50] Berk M, Kapczinski F, Andreazza a C, Dean OM, Giorlando F, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 2011;35:804–17, doi:http://dx.doi.org/10.1016/j.neubiorev.2010.10.001.
[51] Birmaher B, Gill MK, Axelson DA, Goldstein BI, Goldstein TR, Yu H, et al. Longitudinal trajectories and associated baseline predictors in youths with bipolar spectrum disorders. Am J Psychiatry 2014;171:990–9, doi:http://dx.doi.org/10.1176/appi.ajp.2014.13121577.
[52] Yim CY, Soczynska JK, Kennedy SH, Woldeyohannes HO, Brietzke E, McIntyre RS. The effect of overweight/obesity on cognitive function in euthymic individuals with bipolar disorder. Eur Psychiatry 2012;27:223–8, doi:http://dx.doi.org/10.1016/j.eurpsy.2011.02.004.
[53] Depp CA, Strassnig M, Mausbach BT, Bowie CR, Wolyniec P, Thornquist MH, et al. Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. Bipolar Disord 2014;16:422–31, doi:http://dx.doi.org/10.1111/bdi.12200.
[54] Lackner N, Bengesser SA, Birner A, Painold A, Fellendorf FT, Platzer M, et al. Abdominal obesity is associated with impaired cognitive function in euthymic bipolar individuals. World J Biol Psychiatry 2015;1–12, doi:http://dx.doi.org/10.3109/15622975.2015.1046917.
[55] Wilkosc M, Markowska A, Zajac-Lamparska L, Skibinska M, Szalkowska A, Araszkiewicz A. A lack of correlation between brain-derived neurotrophic factor serum level and verbal memory performance in healthy polish population. Front Neural Circuits 2016;10:1–9, doi:http://dx.doi.org/10.3389/fncir.2016.00039.
[56] Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, et al. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J Neurosci 2010;30:5368–75, doi:http://dx.doi.org/10.1523/JNEUROSCI.6251-09.2010.
[57] Niitsu T, Shirayama Y, Matsuzawa D, Hasegawa T, Kanahara N, Hashimoto T, et al. Associations of serum brain-derived neurotrophic factor with cognitive impairments and negative symptoms in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:1836–40, doi:http://dx.doi.org/10.1016/j.pnpbp.2011.09.004.
[58] Kim A, Fagan AM, Goate AM, Benzinger TLS, Morris JC, Head D. Lack of an association of BDNF Val66Met polymorphism and plasma BDNF with hippocampal volume and memory. Cogn Affect Behav Neurosci 2015;15:625–43, doi:http://dx.doi.org/10.3758/s13415-015-0343-x.
[59] Bonaccorso S, Sodhi M, Li J, Bobo WV, Chen Y, Tumuklu M, et al. The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with increased body mass index and insulin resistance measures in bipolar disorder and schizophrenia. Bipolar Disord 2015;17:528–35, doi:http://dx.doi.org/10.1111/bdi.12294.
[60] Grande I, Magalh??es PV, Chendo I, Stertz L, et al. Staging bipolar disorder: clinical, biochemical, and functional correlates. Acta Psychiatr Scand 2014;129:437–44, doi:http://dx.doi.org/10.1111/acps.12268.
[61] Nery FG, Gigante AD, Amaral JA, Fernandes FB, Berutti M, Almeida KM, et al. Serum BDNF levels in unaffected first-degree relatives of patients with bipolar disorder. Rev Bras Psiquiatr 2016;38:197–200, doi:http://dx.doi.org/10.1590/1516-4446-2015-1801.
[62] Rybakowski JK, Suwalska A. Excellent lithium responders have normal cognitive functions and plasma BDNF levels. Int J Neuropsychopharmacol 2010;13:617–22, doi:http://dx.doi.org/10.1017/S1461145710000404.
[63] Mora E, Portella MJ, Forcada I, Vieta E, Mur M. A preliminary longitudinal study on the cognitive and functional outcome of bipolar excellent lithium responders. Compr Psychiatry 2016;71:25–32, doi:http://dx.doi.org/10.1016/j.comppsych.2016.07.008.
[64] D'Addario C, Dell'Osso B, Palazzo MC, Benatti B, Lietti L, Cattaneo E, et al. Selective DNA methylation of BDNF promoter in bipolar disorder: differences

among patients with BDI and BDII. Neuropsychopharmacology 2012;37:1647–55, doi:http://dx.doi.org/10.1038/npp.2012.10.
[65] Carvalho AF, Köhler CA, Fernandes BS, Quevedo J, Miskowiak KW, Brunoni AR, et al. Bias in emerging biomarkers for bipolar disorder. Psychol Med 2016;46:2287–97, doi:http://dx.doi.org/10.1017/S0033291716000957.
[66] Jiménez E, Solé B, Arias B, Mitjans M, Varo C, Reinares M, et al. Impact of childhood trauma on cognitive profile in bipolar disorder. Bipolar Disord 2017;19:363–74, doi:http://dx.doi.org/10.1111/bdi.12514.
[67] Bercik P. The microbiota-gut-brain axis: learning from intestinal bacteria? Gut 2011;60:288–9, doi:http://dx.doi.org/10.1136/gut.2010.226779.
[68] Brietzke E, Mansur RB, Soczynska JK, Kapczinski F, Bressan RA, McIntyre RS. Towards a multifactorial approach for prediction of bipolar disorder in at risk populations. J Affect Disord 2012;140:82–91, doi:http://dx.doi.org/10.1016/j.jad.2012.02.016.
[69] Salagre E, Vieta E, Grande I. El cerebro visceral : trastorno bipolar y microbiota The visceral brain : Bipolar disorder and microbiota. Rev Psiquiatr Salud Ment 2017;3–5 In press.
[70] Fagundes C, Glaser R, Kiecolt-Glaser J. Stressful early life experiences and immune dysregulation across the lifespan. Brain Behav Immun 2013;27:8–12.
[71] Post R, Altshuler L, Leverich G, Frye M, Suppes T, McElroy S, et al. Role of childhood adversity in the development of medical co-morbidities associated with bipolar disorder. J Affect Disord 2013;174:288–94.
[72] Jacka FN, Neil AO, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). BMC Med 2017;15:1–13, doi:http://dx.doi.org/10.1186/s12916-017-0791-y.
[73] Blumberg HP, Kaufman J, Martin A, Whiteman R, Zhang JH, Gore JC, et al. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch Gen Psychiatry 2003;60:1201–8, doi:http://dx.doi.org/10.1001/archpsyc.60.12.1201.
[74] Strasser HC, Lilyestrom J, Ashby ER, Honeycutt NA, Schretlen DJ, Pulver AE, et al. Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study. Biol Psychiatry 2005;57:633–9, doi:http://dx.doi.org/10.1016/j.biopsych.2004.12.009.
[75] Yucel K, McKinnon MC, Taylor VH, Macdonald K, Alda M, Young LT, et al. Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. Psychopharmacology (Berl) 2007;195:357–67, doi:http://dx.doi.org/10.1007/s00213-007-0906-9.
[76] Goodwin G, Vieta E. Effective maintenance treatment - breaking the cycle of bipolar disorder. Eur Psychiatry 2005;20:365–71, doi:http://dx.doi.org/10.1016/j.eurpsy.2005.06.001.
[77] Baldessarini RJ, Salvatore P, H-MK Khalsa, Imaz-Etxeberria H, Gonzalez-Pinto A, et al. Episode cycles with increasing recurrences in first-episode bipolar-I disorder patients. J Affect Disord 2012;136:149–54, doi:http://dx.doi.org/10.1016/j.jad.2011.08.037.
[78] Burdick KE, Russo M, Frangou S, Mahon K, Braga RJ, Shanahan M, et al. Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. Psychol Med 2014;44:3083–96, doi:http://dx.doi.org/10.1017/S0033291714000439.
[79] Martino DJ, Samamé C, Marengo E, Igoa A, Strejilevich SA. A critical overview of the clinical evidence supporting the concept of neuroprogression in bipolar disorder. Psychiatry Res 2016;235:1–6, doi:http://dx.doi.org/10.1016/j.psychres.2015.12.012.
[80] Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. Nat Rev Dis Prim 2018;4:18008, doi:http://dx.doi.org/10.1038/nrdp.2018.8.
[81] Frey BN, Andreazza AC, Houenou J, Jamain S, Goldstein BI, Frye MA, et al. Biomarkers in bipolar disorder : a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. Aust N Z J Psychiatry 2013;47:, doi:http://dx.doi.org/10.1177/0004867413478217.

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