Acute effects of a session of electroconvulsive therapy on brain-derived neurotrophic factor plasma levels

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Running title: Acute effects of ECT in BDNF plasma levels

Conflicts of interest

Dr. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Takeda, Somatics and has obtained research funding from the Ministry of Education, Culture and Sport, the Spanish Ministry of Economy, Industry and Competitiveness (CIBERSAM), by the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017SGR1355), Foundation European Group for Research In Schizophrenia (EGRIS), and the 7th Framework Program of the European Union. Dr. Bioque has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of has received honoraria from talks and/or consultancy of Adamed, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, Pfizer and Sanofi. Dr. Valentí has received research grants from Eli Lilly & Company and has served as a speaker for Abbott, Bristol–Myers Squibb, GlaxoSmithKline, Janssen–Cilag, and Lundbeck. The rest of authors report no competing interests for this study.

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Keywords: Biomarkers; BDNF; Brain-derived neurotrophic factor; ECT; Electroconvulsive therapy.

Abstract

Brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are neurotrophins that play critical roles in brain neuronal function. Previous studies have established the association between BDNF and NGF signalling and severe mental disorders, but changes in BDNF plasma levels and electroconvulsive therapy (ECT) response are controversial. The aim of his study was to explore the acute effects of a single session of ECT on these neurotrophins signalling.

Plasma levels of BDNF and NGF and their tyrosine kinase-type receptors expression in peripheral blood mononuclear cells (PBMCs) were determined before and two hours after a single ECT session in 30 subjects with a severe mental disorder.

Two hours after an ECT session we found a statistically significant decrease of BDNF plasma levels ($p=0.007$). We did not find significant acute effects on NGF plasma levels or receptors expression in PBMCs. We found a significant inverse correlation between the time of convulsion and BDNF plasma levels decrease ($r=-0.041$, $p= 0.024$).

We have identified a decrease in BDNF plasma levels after 2 hours of a single ECT session. These results indicate the interest for future research in the role of neurotrophins in the response and safety of ECT.

Introduction

Electroconvulsive therapy (ECT) is recognized as one of the most effective therapies for certain severe mental disorders resistant to other treatments or in clinical scenarios that need a rapid response [1-6]. Despite its efficacy, it is necessary to expand the available knowledge about its mechanisms of action and to identify useful biological marked linked either to clinical response or to the appearance of side effects.

ECT affect a wide range of molecules, including neurotransmitters, inflammatory pathways and neurotrophic factors [7, 8]. Brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are neurotrophins that play critical roles in neurodevelopment and a wide range of adult neuronal functions [9, 10]. Both BDNF and NGF are activated by their own tyrosine kinase-type receptors, named TrkB and TrkA respectively [11]. In the case of TrkB, two types of receptors have been described: an active full-length form of the receptor (TrkB-F) and a truncated form (TrkB-T). The last one lacks kinase activity and inhibits the TrkB-F function by competing in binding to BDNF [12]. For its part, TrkA mediates on multiple effects of NGF, including neuronal differentiation and programmed death inhibition [11].

Several studies and meta-analyses have established the association between BDNF and NGF signalling and severe mental disorders, including major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ) [13-16]. A meta-analysis conducted by Molendijk et al. concluded that serum BDNF levels were reduced in patients suffering from major depressive disorder (MDD) and in patients receiving a course of antidepressants [17].

Despite a growing number of studies, findings on changes in BDNF levels and the response to ECT are controversial [18]. A recent meta-analysis of 22 studies of BDNF blood levels after ECT in patients with major depressive disorder concluded that BDNF levels may increase after ECT, being a candidate to be used as an indicator of treatment response after one or more weeks of ECT [19]. However, some studies reported that serum or plasma BDNF levels increase at different

time points after ECT [20-29], while other research groups did not find any influence of ECT on BDNF levels [30-35]. Recently, Sorri and collaborators reported a decrease of BDNF levels during the fifth ECT session, between the baseline and the 2-hr samples, with no association between serum or plasma BDNF levels and remission [10]. Finally, baseline serum BDNF levels and the BDNF Val66Met polymorphism did not show any clinical utility in predicting ECT response in treatment-resistant MDD patients [36]. Taken together, these results indicate a need for further research of the effects of ECT on the neurotrophins signalling and of the predictive value of BDNF plasma determination in patients who will receive this treatment.

Considering this background, the main objective of the present study is to explore the acute effects of a single session of ECT on the neurotrophins signalling in a selected group of patients with a severe mental disorder. Besides, we pretend to analyze if there are different effects considering clinical features of the studied sample and ECT parameters.

Subjects and Methods

Subjects

Thirty subjects who attended the Hospital Clínic de Barcelona ECT facilities during the recruitment period were recruited. The study inclusion criteria were: (1) Having a severe mental disorder (Major Depressive Disorder, Bipolar Disorder, Schizophrenia or Schizoaffective Disorder) according to the DSM-5 criteria; and (2) age between 18 and 70 years. The exclusion criteria were the following: (1) being pregnant; (2) presenting acute signs of infection in the previous day, such as fever (>38º) or leukocytosis (> 10,000); (3) being following a treatment of anti-inflammatory drugs, antioxidants, antibiotics or immunological therapies; (4) have been vaccinatedhave in the previous month; and (5) subjects with neurological diseases, traumatic

brain injury with loss of consciousness, mental retardation or generalized developmental disorders history.

All the potential candidates identified during the period of recruitment were discussed in a specific ECT committee and were informed about the study by members of the research group. All participants signed the study informed consent [8]. The study had been approved by the Ethics Committee of the Hospital Clínic de Barcelona (record CB/2017/0369).

Members of the research group collected the study variables from medical records, sociodemographic and clinical data from an interview prior to the ECT session. Participants could be in any ECT regimen (acute: first 6-12 ECT sessions; continuation: first six months of treatment after acute regimen; maintenance: after first six months).

All the ECT stimuli were administered with a MECTA SPECTRUM 5000Q® device (MECTA Corp, Lake Oswego, USA). Adequate ictal response (> 20 seconds, < 60 seconds) were monitored through Electroencephalographic (EEG) and motor seizure registers. Patients underwent the ECT session under a general anesthesia, using Succinylcholine (25–110 mg), atropine (0–1 mg), and sodium tiopenthal (75–400 mg). Before and after the stimulus ventilation was assisted a face mask with high oxygen concentration. Mild hyperventilation was maintained for at least one minute before the brain stimulation. All through the procedure a PHILIPS MP-20 (PHILIPS®, Boeblingen, Germany) Anesthesia monitor was used to monitor non-invasive arterial blood pressure, EKG and heart rate and pulse oximetry. The MECTA EMR® software was used to automatically collect certain characteristics of the stimulation.

Study variables were recorded by the research group members, including age, gender, diagnosis, duration of the illness, information regarding work disability, ECT regimen, ECT electrode placement, EEG time of convulsion and total number of ECT sessions. Prescribed psychopharmacological treatment was also recorded. The prescribed daily doses of antipsychotics were converted to an estimated equivalent amount of chlorpromazine

following the international consensus [37], while the prescribed daily doses of antidepressants were converted to an estimated equivalent amount of fluoxetine following published guidelines [38].

Sample collection and biochemical measurements

10 mL of venous blood samples were collected after overnight fasting before the ECT session (PRE-ECT), and two hours after (Post-ECT) from all participants [8]. In order to be able to compare our results to previous comparable studies that had taken this same measure [10] and to ensure that both measures (pre and post ECT session) were being collected under fasting conditions, we decided to sample at two hours post-ECT. Blood samples were kept in a fridge (at 4ºC) until further manipulation after approximately 1 h. Blood tubes were centrifuged (641 g × 10 min). The separated resultant plasma samples were stored at −80ºC. The rest of the sample was 1:2 diluted in RPMI 1640 (LifeTech) culture medium. A gradient with Ficoll-Paque (GE Healthcare) was used to isolate Peripheral blood mononuclear cells (PBMC) by centrifugation at room temperature (800 g × 40 min). PBMC layer was aspired and resuspended in the culture medium, then centrifuged at room temperature (1116 g × 10 min). Once the supernatant layer was removed, the PBMC-enriched pellet was stored at −80ºC at the Hospital Clinic de Barcelona facilities. Once the whole recruitment was over, all samples were sent to the Neuropsychopharmacology laboratory of the Medicine faculty of the Universidad Complutense de Madrid for subsequent determinations.

Plasma levels of BDNF and NGF were determined using enzymatic assays (ELH-BDNF-1, RayBiotech®; ab99986, abcam), according to the manufacturer's instructions, and measured using a Synergy 2 multi-mode reader (BioTek®). The sensitivity of the assay for BDNF was 80 pg/mL and <14 pg/ml for NGF; for both kits the manufacturer's intra- and interassay

coefficients of variation (CV) were respectively <10% and <12%, while own lab's CVs were <7% and <8%.

Protein levels of TrkA, TrkB-F, and TrkB-T receptors in PBMCs were quantified by Western Blot analysis. In brief, 15 µg of cytosolic extracts were loaded onto electrophoresis gels [39]. Protein samples were separated and transferred onto nitrocellulose membrane (Transfer Pack, Biorad®). After blocking, membranes were incubated with specific antibodies: (1) TrkA, rabbit polyclonal antibody dilution of 1:750 in BSA 1% (sc118, SCB); (2) TrkB-F, rabbit polyclonal antibody dilution of 1:750 in BSA 1% (sc12, SCB); (3) TrkB-T, rabbit polyclonal antibody dilution of 1:1000 in BSA 1% (ab1987, abcam); (4) β-actin mouse monoclonal in a dilution 1:10000 (A5441, Sigma, Spain). Proteins were recognized by the respective horseradish peroxidase-linked secondary antibodies and visualized using an Odyssey® Fc System (Li-COR Biosciences®) and quantified by densitometry (NIH ImageJ® software). Values were normalized to the loading control (β-actin, the blots are shown in figure 1, c-e). All western blots were performed at least three times in separate assays.

Given the counterbalancing effect of TrkB-T and TrkB-F, we decided to choose the ratio of TrkB-F to TrkB-T expression (hereafter F/T ratio) as our index variable for describing BDNF receptor expression.

Statistical analysis

A paired t-test was used to assess the differences of biomarkers expression before and after the ECT session on those variables (TrkA, TrkBF, TrkBT and F/T ratio) which distribution met the assumption of normality in the Kolmogorov-Smirnov (with Lillierfors correction). For those variables which distribution did not met the assumption of normality (BDNF and NGF plasma levels), a nonparametric Wilcoxon Signed Rank test was used.

In order to explore whether certain changes in the neurotrophins expression were associated with some of the demographic, clinical, pharmacological or ECT variables, several sub-analyses were performed. To avoid a large number of post-hoc analyses, only those biomarkers with significant pre/post-ECT activity changes were included in these sub-analyses. Being these exploratory analysis, corrections were not made for multiple comparisons [40]. A mixed between-within subjects analysis of variance was conducted to assess the impact categorical variables on neurotrophins expression. The relationship between the biomarkers variations and continuous variables were investigated using Pearson correlation coefficient. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. The strength of these correlations were evaluated according to Cohen's guidelines (small r=0.10 to 0.29; medium r=0.30 to 0.49; large r=0.50 to 1,) [41].

All analysis with a p-value <0.05 were considered statistically significant. Data were managed and analyzed with the IBM SPSS Statistics (v.23).

Results

Table 1 shows general demographic, clinical, pharmacological and ECT data of all the study participants. There wasn't any recorded incidence during these ECT procedures. Figure 1 summarizes the main results.

Table 1 around here

Figure 1 around here

Table 2 summarizes the changes in neurotrophins plasma levels and in the expression of the receptors in PBMCs before and two 2 hours after the ECT session, when there was a significant decreased of the BDNF plasma levels (from 82.16 ± 6.79 to 63.53 ± 6.75; Z=-2.7, p= 0.007).

Table 2 around here

No baseline (pre-ECT) differences between genders, diagnosis or ECT regimen were found. We found a significant inverse correlation for the EEG time of convulsion and BDNF plasma levels at the endpoint (p= 0.024), with a medium strength of the relationship (r=-0.041).

We conducted group of analyses to explore if the observed changes in BDNF plasma levels after the ECT session were modified by concurrent pharmacological treatment studied. A mixed between-within subjects analysis of variance was conducted to assess the impact of concurrent psychopharmacologic treatment on BDNF levels changes after the ECT session. We did not find significant differences in BDNF levels changes in patients with or without prescriptions of antipsychotic, antidepressant, benzodiazepines, anticonvulsants, lithium or anticholinergics, meaning that changes of BDNF levels were not related to being or not under those treatments. We neither found significant correlation between BDNF plasma levels changes and antipsychotic (p=0.17) or antidepressant (p=0.76) doses.

Discussion

The results of this study point to the acute effects that a single ECT session produces on the neurotrophins pathway. Specifically, two hours after an ECT session we found a statistically significant decrease of the levels of BDNF in plasma (figure 1 a). We also found a significant inverse correlation for the EEG duration of convulsion and BDNF plasma levels decrease (r=-0.041, p= 0.024). We did not find a significant acute effect over NGF plasma levels or receptors expression in PBMCs (figure 1 b-e).

These results agree with previous reports from Sorri and collaborators [10], who recently reported a decrease of BDNF levels between the baseline and the 2-hour samples during the fifth ECT session. Stelzhammer and collaborators also reported decreased serum BDNF levels

after 4 weeks of acute ECT [42]. By contrast, some studies have reported plasma BDNF levels increases at different time points after ECT [20-28]. A recent meta-analysis of 22 studies, revealed no significant changes in the serum BDNF levels between patients who responded and those that did not respond to ECT, but reported a significant increase in the plasma BDNF levels after ECT treatment in the first week and month in patients with MDD [19]. Other research groups did not report any influence of ECT on BDNF plasma levels [30-35].

In our opinion, a major difference between these studies and ours is the timing of blood sampling [10, 42]. In some of studies mentioned above BDNF plasma levels were measured during a course of ECT, while in others blood samples were taken in a variable period of one day to one month after finishing the whole ECT course (generally 9-12 sessions). Besides, previous studies have shown that BDNF levels stored in plasma and serum might differ significantly, which could be a confusion factor that might explain part of the controversial findings so far [19].

Overall, these apparently controversial results sstrengthens the hypothesis that BDNF may undergo differential regulation after different time periods following an ECT course [42]. In that vein, a gene profiling study found increased BDNF expression 2 hours after both acute and chronic ECT, with decreased levels after 6 hours [43]. The mechanisms of action of ECT and psychotropic drugs may be different, so their effects on specific biomarkers of therapeutic response may be different too.

Some limitations should be considered when analyzing these results. First, the relatively small group of participants, which could limit the statistical power of the findings. Secondly, there was heterogeneity of the participants in certain clinical variables such as diagnostics, psychopharmacological treatment or ECT regimen. Thirdly, we studied the effects of a single ECT session over the neurotrophins pathway after two hours, while it would very informative to have re-tested the patients at different moment after the ECT session (i.e. 1 hour, 3 hours, 24 hours, 48 hours, or even one week later) and at the end of the whole acute treatment

(which generally takes between nine and twelve sessions). Fourthly, to our knowledge, the effects of anesthesia, apnea or seizures over the pathway studied are unknown. Finally, we did not have a group of healthy controls paired with the study sample with which to compare the expression of biomarkers at baseline.

Despite these limitations, we believe that our study has identified significant acute effects of ECT treatment over BDNF plasma levels in a group of patients with severe mental disorders. Future studies could identify the optimal time point to determine the levels of BDNF in plasma, serum or even directly from the brain, comparing ECT responders to partinal/non-responders levels across different timepoints during and after ECT treatment [19]. Besides, large genetic consortium such as the International Consortium on the Genetics of Electroconvulsive Therapy and Severe Depressive Disorders (Gen-ECT-ic) may be able to determine the role of the different BDNF genetic polymorphisms in ECT response [44].

In conclusion, and regarding to implications for clinical practice, in this study we have identified a decrease of BDNF plasma levels after 2 hours of an ECT session. Nevertheless, predictive value of BDNF for effects of ECT remains uncertain. The results indicate that this is an area of interest for future research, in which the role of neurothrophins in the response and safety of ECT should be clarified.

Figure 1: Mean differences (SD; univariate analysis) on biomarkers at baseline (Pre) and two hours after (Post) a single electroconvulsive session. BDNF and NGF plasma levels (a, b); Protein expression of TrkA, TrkB-F and TrkB-T in PBMC (c-e); Ratio of TrkB-F/TrkB-T expression (f). BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor; PBMC: Peripheral blood mononuclear cells; TrkA: Tyrosine kinase-type A receptor; TrkB-F: Full-length form of the tyrosine kinase-type B receptor; TrkB-T: Truncated-length form of the tyrosine kinase-type B receptor.

Conflicts of interest

Dr. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Takeda, Somatics and has obtained research funding from the Ministry of Education, Culture and Sport, the Spanish Ministry of Economy, Industry and Competitiveness (CIBERSAM), by the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017SGR1355), Foundation European Group for Research In Schizophrenia (EGRIS), and the 7th Framework Program of the European Union. Dr. Bioque has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of has received honoraria from talks and/or consultancy of Adamed, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, Pfizer and Sanofi. Dr. Valentí has received research grants from Eli Lilly & Company and has served as a speaker for Abbott, Bristol–Myers Squibb, GlaxoSmithKline, Janssen–Cilag, and Lundbeck. The rest of authors report no competing interests for this study.

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Contributors

MBi conducted the literature review, recruited the participants, applied the ECT session, collected data, conducted the main statistical analysis, wrote the first draft of the manuscript and handled subsequent drafts after receiving coauthors feedback. KSMD & CF, performed all biochemical determinations in plasma and in cells and prepared sub-cellular samples, assisted with the analysis and wrote the first draft of the manuscript. AM collected the biological samples and separated plasma and PBMC. EM recruited the participants, collected the blood samples and applied the ECT session. The rest of coauthors participated in the ECT procedures, collected data and commented on drafts. All of the authors contributed to the final version of the paper.

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References

1. The UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *The Lancet* 2017/03/17 2003;361(9360):799-808.

2. Dierckx B, Heijnen WT, van den Broek WW, Birkenhäger TK. Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: a meta-analysis. *Bipolar disorders* 2012;14(2):146-150.

3. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. *Cochrane Database of Systematic Reviews* 2005(2).

4. Bernardo M, Urretavizcaya M. Dignifying Electroconvulsive Therapy based on evidence. *Rev Psiquiatr Salud Ment* Apr-Jun 2015;8(2):51-54.

5. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. *Nature Reviews Disease Primers* 2018 2018;4:18008.

6. Bernardo M, González-Pinto A, Urretavizcaya M. *Consenso Español de Terapia Electroconvulsiva*. Madrid: Sociedad Española de Psiquiatría Biológica; 2018.

7. Wahlund Br, von Rosen D. ECT of Major Depressed Patients in Relation to Biological and Clinical Variables: A Brief Overview. *Neuropsychopharmacology* 2003;28:S21.

8. Bioque M, Mac-Dowell KS, Meseguer A, Macau E, Valero R, Vieta E, Leza JC, Bernardo M. Effects of electroconvulsive therapy in the systemic inflammatory balance of patients with severe mental disorder. *Psychiatry Clin Neurosci* Oct 2019;73(10):628-635.

9. Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: A systematic & quantitative meta-analysis. *Journal of Affective Disorders* 2015;174:432-440.

10. Sorri A, Järventausta K, Kampman O, Lehtimäki K, Bjärkqvist M, Tuohimaa K, et al. Effect of electroconvulsive therapy on brain-derived neurotrophic factor levels in patients with major depressive disorder. *Brain and Behavior* 2018;8(11):e01101.

11. Huang EJ, Reichardt LF. Trk Receptors: Roles in Neuronal Signal Transduction. *Annual Review of Biochemistry* 2019/03/21 2003;72(1):609-642.

12. Carim-Todd L, Bath KG, Fulgenzi G, Yanpallewar S, Jing D, Barrick CA, et al. Endogenous Truncated TrkB.T1 Receptor Regulates Neuronal Complexity and TrkB Kinase Receptor Function In Vivo. *The Journal of Neuroscience* 2009;29(3):678-685.

13. Bocchio-Chiavetto L, Bagnardi V, Zanardini R, Molteni R, Gabriela Nielsen M, Placentino A, et al. Serum and plasma BDNF levels in major depression: A replication study and meta-analyses. *The World Journal of Biological Psychiatry* 2010;11(6):763-773.

14. Fernandes BS, Molendijk ML, Kahler CA, Soares JC, Leite CMGS, Machado-Vieira R, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. *BMC medicine* 2015;13:289-289.

15. Martinez-Cengotitabengoa M, MacDowell KS, Alberich S, Diaz FJ, Garcia-Bueno B, Rodriguez-Jimenez R, et al. BDNF and NGF Signalling in Early Phases of Psychosis: Relationship With Inflammation and Response to Antipsychotics After 1 Year. *Schizophr Bull* Jan 2015;42(1):142-151.

16. Fernandes BS, Steiner J, Berk M, Molendijk ML, Gonzalez-Pinto A, Turck CW, Nardin P, Gonçalves CA. Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications. *Molecular Psychiatry* 2015;20:1108.

17. Molendijk ML, Spinhoven P, Polak M, Bus BAA, Penninx BWJH, Elzinga BM. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N=9484). *Molecular Psychiatry* 2013;19:791.

18. Pinna M, Manchia M, Oppo R, Scano F, Pillai G, Loche AP, Salis P, Minnai GP. Clinical and biological predictors of response to electroconvulsive therapy (ECT): a review. *Neuroscience Letters* 2018;669:32-42.

19. Luan S, Zhou B, Wu Q, Wan H, Li H. Brain-derived neurotrophic factor blood levels after electroconvulsive therapy in patients with major depressive disorder: A systematic review and meta-analysis. *Asian Journal of Psychiatry* 2020;51:101983.

20. Bilgen AE, Bozkurt Zincir S, Zincir S, Özdemir B, Ak M, Aydemir E, Åžener I. Effects of electroconvulsive therapy on serum levels of brain-derived neurotrophic factor and nerve growth factor in treatment resistant major depression. *Brain Research Bulletin* 2014;104:82-87.

21. Bocchio-Chiavetto L, Zanardini R, Bortolomasi M, Abate M, Segala M, Giacopuzzi M, et al. Electroconvulsive Therapy (ECT) increases serum Brain Derived Neurotrophic Factor (BDNF) in drug resistant depressed patients. *European Neuropsychopharmacology* 2006;16(8):620-624.

22. Bumb JM, Aksay SS, Janke C, Kranaster L, Geisel O, Gass P, Hellweg R, Sartorius A. Focus on ECT seizure quality: serum BDNF as a peripheral biomarker in depressed patients. *Eur Arch Psychiatry Clin Neurosci* Apr 2015;265(3):227-232.

23. Haghighi M, Salehi I, Erfani P, Jahangard L, Bajoghli H, Holsboer-Trachsler E, Brand S. Additional ECT increases BDNF-levels in patients suffering from major depressive disorders compared to patients treated with citalopram only. *Journal of Psychiatric Research* 2013;47(7):908-915.

24. Hu Y, Yu X, Yang F, Si T, Wang W, Tan Y, et al. The Level of Serum Brain-Derived Neurotrophic Factor Is Associated With the Therapeutic Efficacy of Modified Electroconvulsive Therapy in Chinese Patients With Depression. *The Journal of ECT* 2010;26(2):121-125.

25. Marano CM, Phatak P, Vemulapalli UR, Sasan A, Nalbandyan MR, Ramanujam S, et al. Increased plasma concentration of brain-derived neurotrophic factor with electroconvulsive therapy: a pilot study in patients with major depression. *J Clin Psychiatry* Apr 2007;68(4):512-517.

26. Okamoto T, Yoshimura R, Ikenouchi-Sugita A, Hori H, Umene-Nakano W, Inoue Y, Ueda N, Nakamura J. Efficacy of electroconvulsive therapy is associated with changing blood levels of homovanillic acid and brain-derived neurotrophic factor (BDNF) in refractory depressed patients: A pilot study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2008;32(5):1185-1190.

27. Piccinni A, Del Debbio A, Medda P, Bianchi C, Roncaglia I, Veltri A, et al. Plasma Brain-Derived Neurotrophic Factor in treatment-resistant depressed patients receiving electroconvulsive therapy. *European Neuropsychopharmacology* 2009;19(5):349-355.

28. Salehi I, Hosseini SM, Haghighi M, Jahangard L, Bajoghli H, Gerber M, et al. Electroconvulsive therapy (ECT) and aerobic exercise training (AET) increased plasma BDNF and ameliorated depressive symptoms in patients suffering from major depressive disorder. *Journal of Psychiatric Research* 2016;76:1-8.

29. Vanicek T, Kranz GS, Vyssoki B, Fugger G, Komorowski A, HÃ¶flich A, et al. Acute and subsequent continuation electroconvulsive therapy elevates serum BDNF levels in patients with major depression. *Brain Stimulation* 2019.

30. Fernandes B, Gama CS, Massuda R, Torres M, Camargo D, Kunz M, et al. Serum brain-derived neurotrophic factor (BDNF) is not associated with response to electroconvulsive therapy (ECT): A pilot study in drug resistant depressed patients. *Neuroscience Letters* 2009;453(3):195-198.

31. Gedge L, Beaudoin A, Lazowski L, du Toit R, Jokic R, Milev R. Effects of Electroconvulsive Therapy and Repetitive Transcranial Magnetic Stimulation on Serum Brain-Derived Neurotrophic Factor Levels in Patients with Depression. *Frontiers in Psychiatry* 2012-February-24 2012;3(12).

32. Gronli O, Stensland GÃy, Wynn R, Olstad R. Neurotrophic factors in serum following ECT: A pilot study. *The World Journal of Biological Psychiatry* 2009;10(4):295-301.

33. Kleimann A, Kotsiari A, Sperling W, Groschl M, Heberlein A, Kahl KG, et al. BDNF serum levels and promoter methylation of BDNF exon I, IV and VI in depressed patients receiving electroconvulsive therapy. *J Neural Transm (Vienna)* Jun 2014;122(6):925-928.

34. Lin CH, Chen MC, Lee WK, Chen CC, Huang CH, Lane HY. Electroconvulsive Therapy Improves Clinical Manifestation with Plasma BDNF Levels Unchanged in Treatment-Resistant Depression Patients. *Neuropsychobiology* 2013;68(2):110-115.

35. Rapinesi C, Kotzalidis GD, Curto M, Serata D, Ferri VR, Scatena P, et al. Electroconvulsive therapy improves clinical manifestations of treatment-resistant depression without changing serum BDNF levels. *Psychiatry Research* 2015;227(2):171-178.

36. Maffioletti E, Gennarelli M, Gainelli G, Bocchio-Chiavetto L, Bortolomasi M, Minelli A. BDNF Genotype and Baseline Serum Levels in Relation to Electroconvulsive Therapy Effectiveness in Treatment-Resistant Depressed Patients. *The Journal of ECT* 2019;Publish Ahead of Print.

37. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am J Psychiatry* Jun 2010;167(6):686-693.

38. Hayasaka Y, Purgato M, Magni LR, Ogawa Y, Takeshima N, Cipriani A, et al. Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. *Journal of Affective Disorders* 2015;180:179-184.

39. Garcia-Bueno B, Bioque M, Mac-Dowell KS, Barcones MF, Martinez-Cengotitabengoa M, Pina-Camacho L, et al. Pro-/anti-inflammatory dysregulation in patients with first episode of psychosis: toward an integrative inflammatory hypothesis of schizophrenia. *Schizophr Bull* Mar 2013;40(2):376-387.

40. Bender R, Lange S. Adjusting for multiple testing--when and how? *J Clin Epidemiol* Apr 2001;54(4):343-349.

41. Cohen J, Cohen P, West SG, Aiken LS. *Applied multiple regression/correlation analysis for the behavioral sciences, 3rd ed*. Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers; 2003.

42. Stelzhammer V, Guest PC, Rothermundt M, Sondermann C, Michael N, Schwarz E, Rahmoune H, Bahn S. Electroconvulsive therapy exerts mainly acute molecular changes in serum of major depressive disorder patients. *European Neuropsychopharmacology* 2013;23(10):1199-1207.

43. Newton SS, Collier EF, Hunsberger J, Adams D, Terwilliger R, Selvanayagam E, Duman RS. Gene Profile of Electroconvulsive Seizures: Induction of Neurotrophic and Angiogenic Factors. *The Journal of Neuroscience* 2003;23(34):10841-10851.

44. Soda T, McLoughlin DM, Clark SR, Oltedal L, Kessler U, Haavik J, et al. International Consortium on the Genetics of Electroconvulsive Therapy and Severe Depressive Disorders (Gen-ECT-ic). *Eur Arch Psychiatry Clin Neurosci* Dec 4 2019.

Tabla (Table)

Table 1. Demographic, clinical characteristics and electroconvulsive therapy parameters

	n=30
Age – years [mean (sd)]	52,97 (16,81)
Gender – no. (%)	
Female	19 (57,7%)
Male	11 (33,3%)
Diagnosis – no. (%)	
Affective Psychosis	24 (80%)
Non-affective Psychosis Diagnosis	6 (20%)
Duration of illness – years [mean (sd)]	19,03 (12,11)
Subjects with an official work disability - no. (%)	26 (76,5%)
ECT regimen – no. (%)	
Acute	6 (20,0%)
Continuation/Maintenance	24 (80%)
ECT application – no. (%)	
Right unilateral	3 (10%)
Bitemporal	27 (90%)
Lifetime ECT number of sessions	60,77 (66,27)
Duration (seconds) of EEG convulsion	40,27 (12,49)
Subjects with psychopharmacological treatments -– no. (%)	
Antidepressants	21 (61.8)
Antipsychotics	25 (73.5)
Benzodiazepines	20 (50.8)
Anticonvulsants	7 (20.6)
Lithium	7 (20.6)
Anticholinergics	3 (8.8)
Fluoxetine equivalent mean daily dose of antidepressants - mg/d (sd)	64.39 (± 36.64)
Chlorpromazine equivalent mean daily dose of antipsychotics - mg/d (sd)	668.21 (± 508.84)

In ECT regimen: “Acute” refers to the first 6-12 ECT sessions, “Continuation” for the following sessions during the first six months and “Maintenance” for the sessions received after this first six-month period. ECT: electroconvulsive therapy; EEG: electroencephalographic.

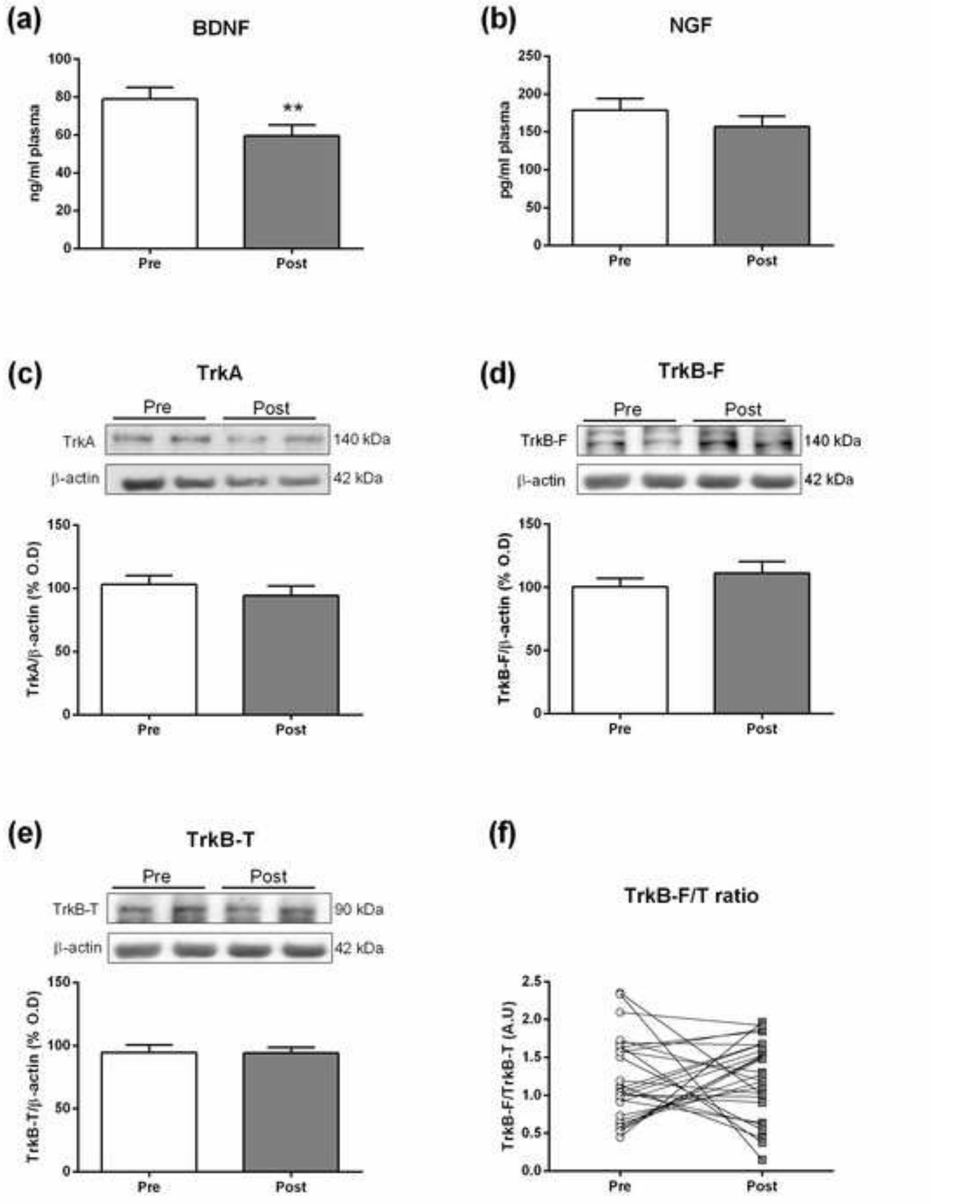
Table 2. Mean differences (± SD) in neurotrophins plasma levels and expression of receptors in PBMCs between pre-ECT and post-ECT session (2 hours after stimulus) in 30 patients with severe mental disorders.

Marker	PRE-ECT	POST-ECT	Statistics	p-value
BDNF $_{\text{plasma, ng/ml}}$	82,16 ± 37,22	63,53 ± 39,99	Z=-2,70	0,007
NGF $_{\text{plasma, pg/ml}}$	178,78 ± 82,39	156,96 ± 76,75	Z=-1,59	0,112
TrkBF $_{\text{WB, \% OD}}$	101,74 ± 36,11	111,86 ±50,04	t=-0,91	0.368
TrkBT $_{\text{WB, \% OD}}$	93,98 ± 34,27	94,12 ± 24,65	t=-0,02	0.986
TrkBF/TrkBT	1,209 ± 0,54	1,22 ±0,51	t=-0,08	0.938
TrkA $_{\text{WB, \% OD}}$	103,07 ± 38,14	95,26 ± 41,49	t=0,82	0.416

Data expressed as mean ± standard deviation. BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor; OD: Optical density; Plasma: plasma levels; TrkA: Tyrosine kinase-type A receptor; TrkBF: Full-length form of the tyrosine kinase-type B receptor; TrkBT: Truncated-length form of the tyrosine kinase-type B receptor; WB: Western Blot. See Methods section for detail.

Figura (Figure)

Pulse aquí para acceder/descargar;Figura (Figure);BDNF ECT - Figure 1.jpg



Conflicts of interest

Dr. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Takeda, Somatics and has obtained research funding from the Ministry of Education, Culture and Sport, the Spanish Ministry of Economy, Industry and Competitiveness (CIBERSAM), by the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017SGR1355), Foundation European Group for Research In Schizophrenia (EGRIS), and the 7th Framework Program of the European Union. Dr. Bioque has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of has received honoraria from talks and/or consultancy of Adamed, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, Pfizer and Sanofi. Dr. Valentí has received research grants from Eli Lilly & Company and has served as a speaker for Abbott, Bristol–Myers Squibb, GlaxoSmithKline, Janssen–Cilag, and Lundbeck. The rest of authors report no competing interests for this study.