

Original article

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

Miquel Bioque^{a,b,c,*}, Karina S. Mac-Dowell^{d,1}, Cristina Font^d, Ana Meseguer^e, Elisabet Macau^f, Marta Garcia-Orellana^g, Marc Valentí^h, Juan C. Leza^{d,*}, Miquel Bernardo^{a,b,c}

^a Barcelona Clínic Schizophrenia Unit, Neuroscience Institute, Hospital Clínic de Barcelona, Barcelona, Spain

^b Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

^c Centro de Investigación Biomédica en red en salud Mental (CIBERSAM), Departament de Medicina, Universitat de Barcelona, Spain

^d Department of Pharmacology & Toxicology, Faculty of Medicine, Universidad Complutense de Madrid University, Instituto de Investigación Hospital 12 de Octubre (i+12), IUIIN; CIBERSAM, Spain

^e Barcelona Clínic Schizophrenia Unit, Neuroscience Institute, Hospital Clínic de Barcelona, Barcelona; CIBERSAM, Spain

^f Psychiatry Department, Neuroscience Institute, Hospital Clínic de Barcelona, Barcelona, Spain

^g Anesthesiology Department, Hospital Clínic de Barcelona, Barcelona; Universitat de Barcelona, Barcelona, Spain

^h Barcelona Bipolar Disorder Program, Psychiatry Department, Neuroscience Institute, Hospital Clínic de Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:

Received 20 April 2020

Accepted 22 May 2020

Available online 14 July 2020

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 signaling 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 signaling.

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 h 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.

© 2020 Sociedad Española de Psiquiatría y Salud Mental (SEPSM). Published by Elsevier España, S.L.U. All rights reserved.

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 markers linked either to clinical response or to the appearance of side effects.

ECT affects 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

* Corresponding authors.

E-mail addresses: mbioque@clinic.cat (M. Bioque), jcleza@med.ucm.es (J.C. Leza).

¹ The first and the second author (MBi and KSMD) contributed equally to this work.

Several studies and meta-analyses have established the association between BDNF and NGF signaling 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-h 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 signaling 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 signaling 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

We recruited 30 subjects who attended an ECT session in the Hospital Clínic de Barcelona following the usual practice in this center, with the following inclusion criteria: (1) meet DSM-5 criteria for a severe mental disorder (Major Depressive Disorder, Bipolar Disorder, Schizophrenia or Schizoaffective Disorder); (2) age between 18 and 70 years; and (3) be able to sign the informed consent. Participants could be in any ECT regimen (acute or continuation/maintenance). The exclusion criteria were: (1) being pregnant; (2) be in treatment with anti-inflammatory drugs (including steroids), antioxidants, antibiotics or immunological therapies; (3) present fever ($>38^{\circ}$) or leukocytosis ($>10,000$) in the previous 24 h; (4) have received a vaccine in the previous 4 weeks; and (5) present a history of neurological diseases, a history of traumatic brain injury with loss of consciousness, mental retardation or generalized developmental disorders.

All the subjects who met the inclusion/exclusion criteria during the period of recruitment were discussed in a specific ECT committee and were informed about the study by members of the research group, obtaining the informed consent from all participants.⁸ Together with the medical records, sociodemographic and clinical data of the patients were collected in an interview prior to the ECT session. The study had been approved by the Ethics Committee of the Hospital Clínic de Barcelona (record CB/2017/0369).

A MECTA SPECTRUM 5000Q[®] device (MECTA Corp, Lake Oswego, USA) was used for all the ECT stimuli administration. Electroencephalographic (EEG) and motor seizure manifestations were monitored to ensure that an adequate ictal response occurred (>20 s) or to detect prolonged seizure activity. Patients were

continuously monitored (non-invasive arterial blood pressure, EKG and heart rate and pulse oximetry) using a PHILIPS MP-20 Anesthesia monitor (PHILIPS[®], Boeblingen, Germany). Succinylcholine (30–120 mg), atropine (0–1 mg), and sodium tiopental (75–450 mg) were used for general anesthesia. Ventilation was assisted with face mask at high oxygen concentration before and after the stimulus and mild hyperventilation was maintained for at least one minute before the electrical stimuli. The characteristics of the electrical stimulus were automatically recorded by the MECTA EMR[®] software connected to the stimulator. Patients 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).

Demographic characteristics of the patients (age, gender), diagnosis, duration of the illness, information regarding work disability, ECT regimen (acute, continuation or maintenance), electrode placement, EEG time of convulsion and total number of lifetime ECT sessions were recorded. 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

Venous blood samples (10 mL) were collected between 8:30 h and 9:30 h (Pre-ECT), after overnight fasting, and two hours after the stimulation (Post-ECT).⁸ We decided to sample at two hours post-ECT 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.⁸ Samples were maintained at 4°C until preparation after approximately 1 h. Blood tubes were centrifuged ($641\text{ g} \times 10\text{ min}$). The resultant plasma samples were collected and stored at -80°C . The rest of the sample was 1:2 diluted in culture medium (RPMI 1640, LifeTech) and a gradient with Ficoll-Paque (GE Healthcare) was used to isolate mononuclear cells by centrifugation ($800\text{ g} \times 40\text{ min}$, room temperature [RT]). Peripheral blood mononuclear cells (PBMC) layer was aspirated and resuspended in RPMI and centrifuged ($1116\text{ g} \times 10\text{ min}$, RT). The supernatant was removed, and the mononuclear cell-enriched pellet was stored at -80°C . Once the whole sample recruitment was finished in Hospital Clínic de Barcelona, all samples were sent to Universidad Complutense de Madrid for subsequent ELISA and Western Blot 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 $<14\text{ pg/mL}$ 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, $15\text{ }\mu\text{g}$ 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 1:10,000 (A5441, Sigma, Spain). Proteins were recognized by the respective

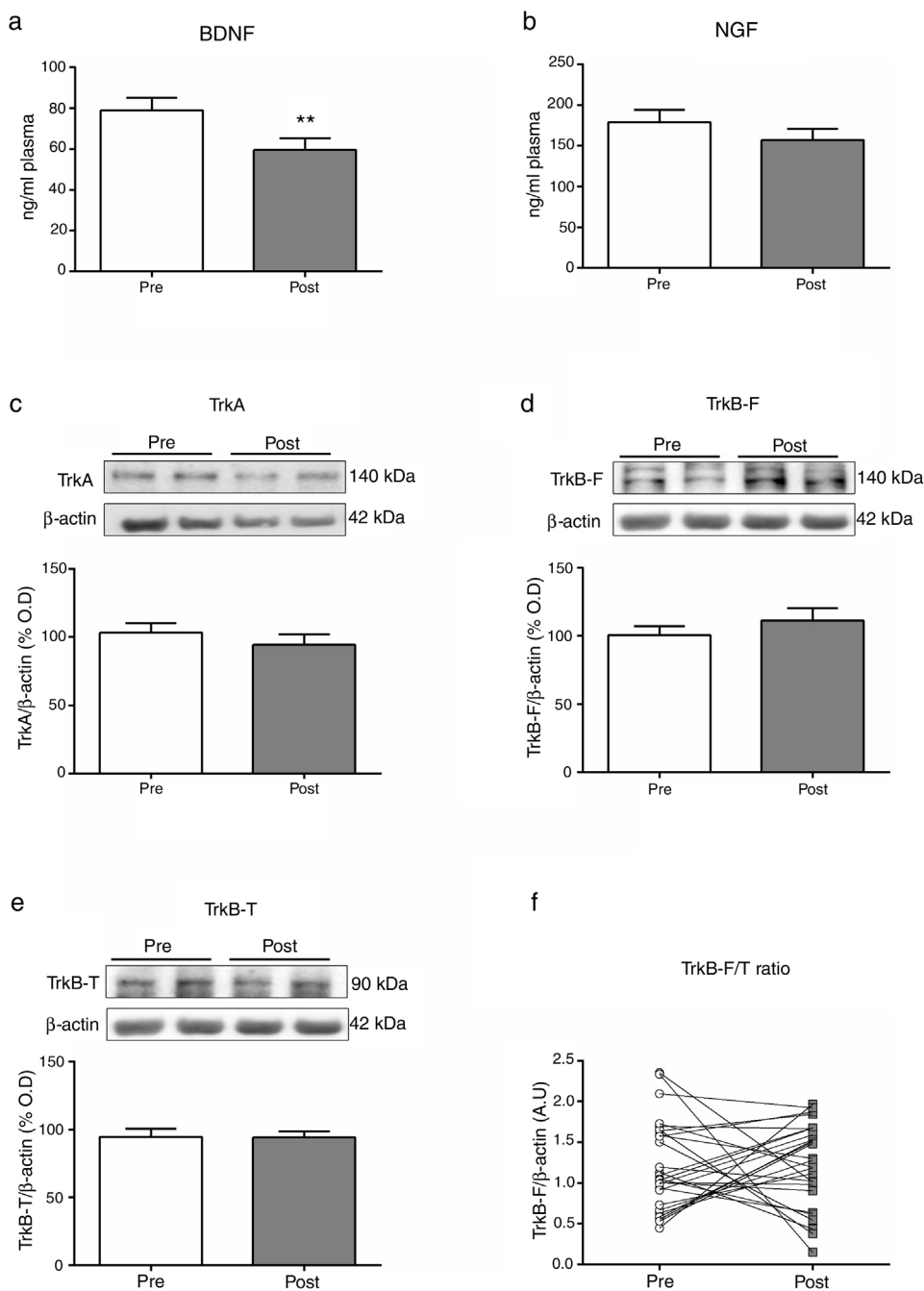


Fig. 1. Mean differences (SD; univariate analysis) on biomarkers at baseline (Pre) and two hours after (Post) a single electroconvulsive session. BDNF and NGF plasma levels (a, b); Protein expression of TrkA, TrkB-F and TrkB-T in PBMC (c-e); Ratio of TrkB-F/TrkB-T expression (f). BDNF: Brain-derived 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.

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 Fig. 1c–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

Differences in biomarkers expression before and after the ECT session were assessed using a paired t-test on those variables (TrkA, TrkB-F, TrkB-T and F/T ratio) which distribution met the assumption of normality in the Kolmogorov-Smirnov (with Lilliefors correction) test. For BDNF and NGF plasma levels analysis, a non-parametric Wilcoxon Signed Rank test was used.

Several sub-analyses were performed to explore whether the changes in the expression of biomarkers were associated with some

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.

of the sociodemographic, clinical or treatment characteristics of ECT. To limit the number of post hoc analyses, we only explored the changes in those biomarkers with significant changes in the activity. Thus, a mixed between-within subjects analysis of variance was conducted to assess the impact categorical variables (gender, diagnosis, ECT regimen, electrodes placement, prescribed treatment) on these biomarkers expression. The relationship between the biomarkers changes 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 $r = 0.10$ – 0.29 ; medium $r = 0.30$ – 0.49 ; large $r = 0.50$ – 1).⁴⁰ Being these exploratory analysis, corrections were not made for multiple comparisons.⁴¹

A value of $p < 0.05$ was taken to be statistically significant in all analysis. Data were managed and analyzed with the IBM SPSS Statistics v.23.

Results

Table 1 shows general demographic, clinical and ECT parameters data of the 30 participants included in the study. No incidences were recorded during the ECT procedures in these patients. The graphic representation of the main results is summarized in Fig. 1.

Table 2 summarizes the changes in neurotrophins plasma levels and in the expression of the receptors in PBMCs before and two 2 h after the ECT session, when there was a significant decreased of

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 _{plasma} , ng/ml	82.16 ± 37.22	63.53 ± 39.99	Z = -2.70	0.007
NGF _{plasma} , pg/ml	178.78 ± 82.39	156.96 ± 76.75	Z = -1.59	0.112
TrkB _{WB} , % OD	101.74 ± 36.11	111.86 ± 50.04	t = -0.91	0.368
TrkB _{TWB} , % OD	93.98 ± 34.27	94.12 ± 24.65	t = -0.02	0.986
TrkB _F /TrkB _T	1.209 ± 0.54	1.22 ± 0.51	t = -0.08	0.938
TrkA _{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; TrkB_F: Full-length form of the tyrosine kinase-type B receptor; TrkB_T: Truncated-length form of the tyrosine kinase-type B receptor; WB: Western Blot. See Methods section for detail.

the BDNF plasma levels (from 82.16 ± 6.79 to 63.53 ± 6.75; Z = -2.7, $p = 0.007$).

There were no baseline (pre-stimulation) differences between genders, diagnosis (affective disorders vs. schizophrenia related disorders) or ECT regimen (acute vs. continuation/maintenance). We carried out a series of exploratory sub-analyses to detect whether the significant changes in BDNF plasmatic levels were associated with certain sociodemographic, clinical or ECT treatment characteristics. 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 (Fig. 1a). 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 (Fig. 1b–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-h 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.²¹ 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 explain in part the controversial findings so far.¹⁹

Overall, these apparently controversial results are consistent with the hypothesis that BDNF undergoes differential regulation after different time periods following ECT.⁴² In that vein, a gene profiling study found increased BDNF expression 2 h after both acute and chronic ECT, with decreased levels after 6 h.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 sample size, which could be limiting the statistical power. Secondly, we studied the effects of a single ECT session after two hours, while it would very informative to have re-tested the patients at different moment after the ECT session (i.e. 1 h, 3 h, 24 h, 48 h, or even one week later) and at the end of the whole acute treatment (generally 9–12 sessions). Thirdly, there was heterogeneity of the subjects included in the study in clinical variables such as diagnostics, psychopharmacological treatment or ECT regimen. Fourthly, we do not know the effects of anesthesia, the apnea time or of the tonic-clonic seizures on the pathway studied. 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, which deserve more attention in future research. Future studies could identify the optimal time point to predict the levels of BDNF in plasma, serum or even directly from the brain, comparing favorable responders, partial responders, and non-responders for plasma and serum BDNF levels across different timepoints during and after ECT treatment.²¹ 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 h 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 neurotrophins in the response and safety of ECT should be clarified.

Authors' 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.

Funding

This study was supported by Instituto de Salud Carlos III, Fondo Europeo de Desarrollo Regional, Unión Europea, “Una manera de hacer Europa”; MINECO SAF2016/75500-R; Centro de Investigación Biomédica en Red de salud Mental, CIBERSAM, and by Generalitat de Catalunya and Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2014SGR441 and 2014SGR398).

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.

Acknowledgments

Authors want to acknowledge Sonia Hernández and all the members of the neuroanesthesia section at the Hospital Clínic de Barcelona.

References

1. The UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. 2003;361:799–808.
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 Disord*. 2012;14:146–150.
3. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. *Cochrane Database Syst Rev*. 2005.
4. Bernardo M, Urretavizcaya M. Dignifying electroconvulsive therapy based on evidence. *Rev Psiquiatr Salud Ment*. 2015;8:51–54.
5. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. *Nat Rev Dis Prim*. 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, et al. Effects of electroconvulsive therapy in the systemic inflammatory balance of patients with severe mental disorder. *Psychiatry Clin Neurosci*. 2019;73:628–635.
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. *J Affect Disord*. 2015;174:432–440.
10. Sorri A, Järventausta K, Kampman O, et al. Effect of electroconvulsive therapy on brain-derived neurotrophic factor levels in patients with major depressive disorder. *Brain Behav*. 2018;8:e01101.
11. Huang EJ, Reichardt LF. Trk receptors: roles in neuronal signal transduction. *Annu Rev Biochem*. 2003;72:609–642.
12. Carim-Todd L, Bath KG, Fulgenzi G, et al. Endogenous truncated TrkB.T1 receptor regulates neuronal complexity and TrkB kinase receptor function – in vivo. *J Neurosci*. 2009;29:678–685.
13. Bocchio-Chiavetto L, Bagnardi V, Zanardini R, et al. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. *World J Biol Psychiatry*. 2010;11:763–773.

14. Fernandes BS, Molendijk ML, Kahler CA, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. *BMC Med.* 2015;13:289.
15. Martinez-Cengotitabengoa M, MacDowell KS, Alberich S, et al. BDNF and NGF signalling in early phases of psychosis: relationship with inflammation and response to antipsychotics after 1 year. *Schizophr Bull.* 2015;42:142–151.
16. Fernandes BS, Steiner J, Berk M, et al. Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications. *Mol Psychiatry.* 2015;20:1108.
17. Molendijk ML, Spinhoven P, Polak M, et al. Concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations ($N = 9484$). *Mol Psychiatry.* 2013;19:791.
18. Pinna M, Manchia M, Oppo R, et al. Clinical and biological predictors of response to electroconvulsive therapy (ECT): a review. *Neurosci Lett.* 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 J Psychiatry.* 2020;51:101983.
20. Bilgen AE, Bozkurt Zincir S, Zincir S, et al. Effects of electroconvulsive therapy on serum levels of brain-derived neurotrophic factor and nerve growth factor in treatment resistant major depression. *Brain Res Bull.* 2014;104:82–87.
21. Bocchio-Chiavetto L, Zanardini R, Bortolomasi M, et al. Electroconvulsive Therapy (ECT) increases serum Brain Derived Neurotrophic Factor (BDNF) in drug resistant depressed patients. *Eur Neuropsychopharmacol.* 2006;16:620–624.
22. Bumb JM, Aksay SS, Janke C, et al. Focus on ECT seizure quality: serum BDNF as a peripheral biomarker in depressed patients. *Eur Arch Psychiatry Clin Neurosci.* 2015;265:227–232.
23. Haghghi M, Salehi I, Erfani P, et al. Additional ECT increases BDNF-levels in patients suffering from major depressive disorders compared to patients treated with citalopram only. *J Psychiatr Res.* 2013;47:908–915.
24. Hu Y, Yu X, Yang F, 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. *J ECT.* 2010;26:121–125.
25. Marano CM, Phatak P, Vemulapalli UR, et al. Increased plasma concentration of brain-derived neurotrophic factor with electroconvulsive therapy: a pilot study in patients with major depression. *J Clin Psychiatry.* 2007;68:512–517.
26. Okamoto T, Yoshimura R, Ikenouchi-Sugita A, et al. 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. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32:1185–1190.
27. Piccinni A, Del Debbio A, Medda P, et al. Plasma Brain-Derived Neurotrophic Factor in treatment-resistant depressed patients receiving electroconvulsive therapy. *Eur Neuropsychopharmacol.* 2009;19:349–355.
28. Salehi I, Hosseini SM, Haghghi 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. *J Psychiatr Res.* 2016;76:1–8.
29. Vanicek T, Kranz GS, Vyssoki B, et al. Acute and subsequent continuation electroconvulsive therapy elevates serum BDNF levels in patients with major depression. *Brain Stimul.* 2019.
30. Fernandes B, Gama CS, Massuda R, 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. *Neurosci Lett.* 2009;453:195–198.
31. Gedde 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. *Front Psychiatry.* 2012;3.
32. Gronli O, Stensland GÅY, Wynn R, Olstad R. Neurotrophic factors in serum following ECT: a pilot study. *World J Biol Psychiatry.* 2009;10:295–301.
33. Kleimann A, Kotsiari A, Sperling W, 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).* 2014;122:925–928.
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;68:110–115.
35. Rapinesi C, Kotzalidis GD, Curto M, et al. Electroconvulsive therapy improves clinical manifestations of treatment-resistant depression without changing serum BDNF levels. *Psychiatry Res.* 2015;227:171–178.
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. *J 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.* 2010;167:686–693.
38. Hayasaka Y, Purgato M, Magni LR, et al. Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. *J Affect Disord.* 2015;180:179–184.
39. Garcia-Bueno B, Bioque M, Mac-Dowell KS, et al. Pro-/anti-inflammatory dysregulation in patients with first episode of psychosis: toward an integrative inflammatory hypothesis of schizophrenia. *Schizophr Bull.* 2013;40:376–387.
40. 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.
41. Bender R, Lange S. Adjusting for multiple testing – when and how? *J Clin Epidemiol.* 2001;54:343–349.
42. Stelzhammer V, Guest PC, Rothermundt M, et al. Electroconvulsive therapy exerts mainly acute molecular changes in serum of major depressive disorder patients. *Eur Neuropsychopharmacol.* 2013;23:1199–1207.
43. Newton SS, Collier EF, Hunsberger J, et al. Gene profile of electroconvulsive seizures: induction of neurotrophic and angiogenic factors. *J Neurosci.* 2003;23:10841–10851.
44. Soda T, McLoughlin DM, Clark SR, et al. International consortium on the genetics of electroconvulsive therapy and severe depressive disorders (Gen-ECT-IC). *Eur Arch Psychiatry Clin Neurosci.* 2019;4.