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Changes in serum levels of brain-derived neurotrophic factor with electroconvulsive therapy and pharmacotherapy and its clinical correlates in male schizophrenia patients

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Original Article

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Abstract

Objectives: It has been postulated that neurotrophin dysregulation leads to disorganisation in neuronal networks, which results in schizophrenia. The current study sets out to evaluate if the finding of lower brain-derived neurotrophic factor (BDNF) levels in schizophrenia patients could be confirmed in an independent cohort and to investigate if the BDNF levels can be altered with different treatment modalities such as electroconvulsive therapy (ECT) and/or antipsychotic pharmacotherapy (PT). *Methods:* A total of 54 male patients with schizophrenia and 35 healthy controls were included in the study. Schizophrenia patients were subdivided into two groups as the ones who underwent ECT + PT and only PT. Clinical and sociodemographic data questionnaire, Positive and Negative Syndrome Scale (PANSS) and blood sample collection for BDNF assessment were applied to all patients (on first and last days of admissions) and healthy participants (on the day of the interview). Then, clinical parameters and blood sample outcomes were statistically analysed. *Results:* Mean BDNF levels of healthy individuals were significantly higher than mean pre- and post-treatment BDNF levels in both PT only and ECT + PT groups. While serum BDNF levels did not increase after ECT + PT, there was a trend level increase in the PT only group. There was no significant correlation between the changes in serum BDNF levels with total PANSS scores in either group after treatment. *Conclusions:* We could confirm previously suggested data of lower serum BDNF levels in schizophrenia patients compared to healthy population but we could not find significant increase in serum BDNF levels with ECT + PT or only PT as some previous studies suggested.

Significant outcomes

- Serum BDNF levels of schizophrenia patients in both PT only and ECT + PT groups were lower than healthy controls both before and after treatment.
- Serum BDNF levels did not increase after treatment in both ECT + PT and PT only groups. Trend level increase was seen in the PT only group, though.
- No significant relationship could be identified between the change in BDNF levels and the change in PANSS scores in both ECT + PT and PT only groups.
- Post-treatment BDNF levels were higher in the PT group compared to the ECT + PT group.

Limitations

- The main drawback of the current study is the comparatively low number of patients in the ECT + PT group. Financial restrictions and closure of the ECT unit at the hospital where the study was conducted due to preventive measures taken after the COVID-19 outbreak are the main reasons for the low recruitment of patients in ECT + PT group.
- The effect of treatment solely with ECT could not be assessed because the patients undergoing ECT were also treated with PT.
- BMI and smoking status which affect BDNF levels have not been questioned.
- The average hospital stay was 28 days for the ECT group and 19 days for the PT group. This suggests that the change in BDNF levels estimated in this study is only the acute (not subacute or chronic) response of the patients to both treatments.

Introduction

Brain-derived neurotrophic factor (BDNF) is an important member of the neurotrophin family of growth factors and plays a significant role in neurodevelopment, survival and function of neurons, as well as synaptic plasticity (Bathina & Das, 2015). Previous studies have shown that it is indeed likely that BDNF plays a role in schizophrenia. A number of clinical trials measuring BDNF levels in serum and plasma have been conducted in the last 20 years. When the recent literature is carefully evaluated, consistent data are observed on a reduction in peripheral BDNF levels in schizophrenia patients compared to healthy individuals (Koeva *et al.*, 2014; Valiente-Gomez *et al.*, 2014; Song *et al.*, 2015; Akyol *et al.*, 2015; Simsek *et al.*, 2015; Chiou & Huang, 2016; Li *et al.*, 2016; Bakirhan *et al.*, 2017; Islam *et al.*, 2017; Li *et al.*, 2018; Weickert *et al.*, 2019).

Post-mortem brain studies in schizophrenia samples reported low levels of BDNF not only in peripheral blood but also in the brain tissue (Weickert *et al.*, 2003; Ray *et al.*, 2014). Based on these results, a low BDNF level is likely to mediate in the neurodevelopmental pathway of schizophrenia by affecting new neuron development, synaptogenesis and inter-neuronal communication. Considering all the information above one may also therefore hypothesise that BDNF levels can increase upon recovery of the patients. A meta-analysis reported that plasma (but not serum) BDNF levels in schizophrenia patients showed an increase after pharmaceutical treatment, independent of the dosage of antipsychotic drugs or the presence of a response to antipsychotic drugs (Fernandes *et al.*, 2015). Yet another recent study demonstrated that serum BNDF levels were significantly increased in schizophrenic patients who were institutionalised and regularly medicated for a long time (10 years at least) when compared to healthy control subjects (Reis *et al.*, 2008).

Electroconvulsive seizures have also been reported to increase BDNF mRNA and protein levels in the rat brain (Begni *et al.*, 2016). To our knowledge, the studies by Li *et al.* (2016), who found an effect of ECT on BDNF levels and Fernandes *et al.* (2010) who did not find any effect of ECT on BDNF levels, are the only papers available in the published literature which examined the relationship between drug therapy, ECT and peripheral BDNF levels in schizophrenia patients. The significance of the current study is therefore further enhanced by the fact that the association between ECT and BDNF levels in schizophrenia patients has not been adequately addressed in the literature.

We believe this to be one of the most important shortcomings in the field. By reviewing surveys showing more effective treatment of schizophrenia with ECT such as those carried out by Petrides *et al.* and Chan *et al.*, we expected BDNF levels to reach higher levels in the ECT patients compared to the pharmacotherapy (PT) group before beginning of the study (Petrides *et al.*, 2015, Chan *et al.*, 2019).

To test this hypothesis, four central objectives were identified in the current study: (1) to determine and compare pre-treatment (pharmaceutical and electroconvulsive) serum BDNF levels of schizophrenic male patients and healthy controls, (2) to determine and compare post-treatment serum BDNF levels of male schizophrenia patients and healthy controls, (3) to determine and compare the change in serum BDNF levels after treatment with PT and ECT, and (4) to ascertain the presence of any relation between the extent of change in serum BDNF levels and the specific treatment method.

Methods

Study population

A total of 54 schizophrenia patients were recruited for the study. All patients were selected among recently admitted inpatients experiencing symptomatic exacerbation. The recruitment protocol lasted from December 2019 to July 2020. Participants were selected from inpatients admitted to the psychiatric wards of Bakirkoy Research and Training Hospital and approached for participation in the study. Written informed consent was obtained from the participants or their caregivers. Diagnosis was based on DSM-5 criteria and all patients were interviewed in person by a trained psychiatrist. The ECT group consisted of 19 patients (all male; mean age: 32.47 ± 9.53 years, range: 18–51 years) who were referred for ECT at the Department of Psychiatry, Bakirkoy Research and Training Hospital, Istanbul, Turkey; all of these patients were also treated with antipsychotics. The PT group included 35 patients (all male; mean age: 35.23 ± 11.64 years, range: 19–63 years) who received antipsychotic drug treatment at the hospital. Fifty-eight schizophrenia patients were initially recruited to the study, but during the process, 4 patients were excluded. Two of these patients were understood to have mental retardation when a careful investigation of past medical records was carried out. One patient had myocardial infarction during his hospital stay and one patient had his diagnosis changed to schizoaffective disorder. The control group consisted of 35 healthy individuals without any history of psychiatric disorders. The healthy individuals were selected from among the hospital staff. Individuals diagnosed with an additional psychiatric disorder such as alcohol and/or substance abuse, mental retardation, dementia or other organic mental disorders, in addition to those diagnosed with a comorbid general medical condition such as hypothyroidism, epilepsy, diabetes mellitus or cardiovascular disease were not included in the study. The study protocol was approved by the Bakirkoy Research and Training Hospital Ethics Committee (IRB Date and Number: 05.11.2019/396).

Electroconvulsive therapy

All subjects underwent standard clinical evaluation including internal medicine and anaesthesia consultations prior to ECT. The ECT sessions were scheduled between 09 : 00 and 12 : 00 and were conducted with the Thymatron System IV (Somatics, Inc, Lake Bluff, IL, USA) device with two-ended short pulse, square wave standard technique, by bitemporal placement of electrodes. Motor convulsions and induced tachycardia were monitored and electroencephalograms were recorded during ECT. The total number of ECT sessions was determined by the treating physician. Patients who were on antiepileptic drugs were already excluded from the study; nonetheless, all benzodiazepine group of drugs were discontinued 24 h before the ECT session. General anaesthesia was induced by the anaesthesiologist, often with IV propofol (0.75–1 mg/kg) and succinylcholine (0.5 mg/kg). A maximum of three consecutive attempts were made to achieve adequate (25 s minimum) seizure per session. Patients' respiration was provided using positive pressure ventilation with 100% oxygen. After ECT application, the patients were kept in the recovery room until their vital signs stabilised, and then they were transferred from the ECT centre to the psychiatric services.

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Symptom ratings

All patients who participated in the current study and their legal representatives/relatives were informed of the study's purpose and an informed consent form was filled. After approval, a clinical and sociodemographic data sheet which included information like age of illness onset (years), duration of illness (years), number of ECT sessions applied in past admissions, duration of untreated psychosis (months), number of past suicide attempts, chlorpromazine equivalent dose of current antipsychotic taken during the study (mg/daily) and duration of current admission (days). The Positive and Negative Syndrome Scale (PANSS), which is a clinical instrument principally developed for use in schizophrenia patients to identify the presence and severity of psychopathology symptoms, was applied to all patients by a psychiatrist who had already received training to perform the scale. Sum scores of the PANSS results were used. Patients undergoing ECT were examined twice: once before starting ECT and again within 3 days after completing the sessions and the latter also coincided with the decision to discharge these patients. Those patients treated only with antipsychotic drugs were also examined twice: once before starting antipsychotic treatment and later after the decision to discharge the patient was made.

Brain-derived neurotrophic factor

After overnight fasting, pre-prandial blood samples were collected between 06 : 00 and 07 : 00 h on the same schedule as symptom assessment. For healthy controls, a baseline blood sample was collected on the morning of the visit. For patients receiving ECT, a baseline blood sample was collected on the morning of the first session and post-treatment serum was obtained within 3 days of the last session. Blood samples were obtained from patients in the PT group twice, once on the first morning of hospitalisation and later on the first morning after the decision to discharge was made. Serum samples were separated by centrifugation (3000 rpm for 10 min at 20°C) and stored at −80°C. The duration of storage of the blood samples varied from 3 days to 6 months. The BDNF concentration was measured with an enzyme-linked immunosorbent assay (ELISA) using the Human Brain Derived Neurotrophic Factor ELISA Kit (Bioassay Technology Laboratory, Catalog no: E1302Hu) and results are presented as ng/ml.

Statistics

Descriptive analyses such as percentile (25th–75th) and median were used to evaluate the demographic and clinical characteristics of schizophrenia patients and healthy controls. The average BDNF levels were evaluated for normal distribution hypothesis in all three groups. Since BDNF levels were not distributed normally and the number of participants in each groups did not exceed 60, BDNF data between the three groups were compared with the Kruskal Wallis test. Bonferroni correction in post hoc test was not performed because of the use of nonparametric analysis for post hoc paired comparisons. Chi-Square analysis and Fisher's exact Chi-Square analysis (where proportional data were less than 5%) were used in the proportional comparison of categorical variables between all three groups. The amount of pre- and post-treatment change in BDNF levels in ECT and PT groups was examined by Wilcoxon test. Relationships between BDNF levels, clinical and psychometric characteristics were examined by Spearman correlation analysis. The differences in age at onset of illness, duration of illness, duration of past admissions, number of ECT sessions applied during past admissions, duration of untreated psychosis, number of past suicide attempts, mean chlorpromazine equivalent dose of current antipsychotics and duration of current admission between the study groups were evaluated by Mann Whitney U test. The normal distribution of the data was assessed on the basis of whether the skewness and kurtosis values were in the range of ±1.5. Multiple linear regression analysis was used to examine the clinical and psychometric parameters that could predict the change in BDNF scores in patients with schizophrenia. The significance level for all analyses was set at $p < 0.05$. IBM SPSS statistics 20 was used to analyse the data.

Results

Demographic and clinical data

According to the Kruskal Wallis H test, the mean age of the control group (40.51 ± 7.16 years), ECT group (32.47 ± 9.53 years) and PT only group (35.23 ± 11.64 years) was found to be significantly different ($\chi^2 = 11.45$, $p = 0.003$). In addition, according to paired comparisons, the mean age of the control group was higher than the mean age of the ECT group ($Z = -2.99$; $p = 0.003$) and PT only group ($t = -2.29$; $p < 0.025$). Twenty-nine (82.9%) patients in the PT only group and 15 (78.9%) patients in ECT group had a history of previous suicide attempts; this difference, however, did not reach statistical significance ($\chi^2 = 0.13$, $p = 0.724$, Pearson Chi-Square analysis).

The demographic and clinical characteristics of the study population are summarised in Table 1. We observed that the mean duration of previous hospitalisations ($Z = -3.79$, $p < 0.001$) was significantly higher in the PT group compared to the ECT group, while the mean number of ECT sessions applied during past admissions ($Z = -4.44$, $p < 0.001$), mean chlorpromazine equivalent dose of current antipsychotics ($Z = -2.90$, $p = 0.004$) and the mean duration of the current admission ($Z = -3.35$, $p = 0.001$) were significantly higher in the ECT group compared to the PT group. According to patient records, 17 participants were already receiving medication prior to their inclusion in the study. Nine of these 17 patients were assigned to the PT group, while 8 were assigned to the ECT group. The admission of all patients recruited in the current study to the psychiatry ward was compulsory; reports from families of these patients indicated irregular medication use as a habit of these patients. This spurious information was likely to obfuscate the findings of the current study, and the data were therefore disregarded in statistical analyses. Other patients were not on any medication prior to admission to the psychiatry ward. The median value of the total PANSS score was 108.21 ± 16.04 in the ECT group prior to ECT; this value decreased to 65.16 ± 11.76 after ECT. The median of the total PANSS score was 110.49 ± 22.19 in the PT group before medication and decreased to 63.54 ± 15.63 after medication. The decrease in the PANSS scores for both groups reached statistical significance. No significant difference in clinical parameters or a significant relationship between these clinical parameters and serum BDNF levels could be identified between the two patient groups, neither before nor after treatment (Table 1). Eighty-six percentage of the patients who underwent ECT were referred to the hospital due to non-response to other treatments.

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Table 1. Comparison of study groups in terms of clinical and psychometric properties

	Schizophrenia patients ECT (n = 19)	Schizophrenia patients PT (n = 35)	
	Median (25th–75th)	Median (25th–75th)	*P*
Age of illness onset (years)	22.00 (19.00–24.00)	22.00 (18.00–28.00)	0.744[a]
Duration of illness (years)	7.00 (4.00–19.00)	9.00 (5.00–18.00)	0.393[a]
Duration of current admission (days)	25.00 (18.00–39.00)	16.00 (14.00–22.0)	0.001[a]
Duration of past admissions (days)	0.00 (0.00–9.00)	45.00 (13.00–174.00)	<0.001[a]
Number of ECT sessions applied in previous admissions	64.00 (3.00–191.00)	0.00 (0.00–7.00)	<0.001[a]
Duration of untreated psychosis (months)	12.00 (3.00–36.00)	12.00 (7.00–36.00)	0.383[a]
Chlorpromazine equivalent dose of current antipsychotic taken during the study (mg/day)	1561.00 (1073.00–1928.00)	1054.00 (781.00–1271.00)	0.004[a]

	Before ECT (n = 19)	After ECT (n = 19)		Before Medication (n = 35)	After Medication (n = 35)	
	Median (25th–75th)	Median (25th–75th)	*P*	Median (25th–75th)	Median (25th–75th)	*P*
Total PANSS score	102.00 (99.00–118.00)	63.00 (56.00–69.00)	<0.001[b]	108.00 (97.00–128.00)	62.00 (50.00–71.00)	<0.001[b]
Positive PANSS score	35.00 (29.00–39.00)	18.00 (13.00–19.00)	<0.001[b]	35.00 (29.00–36.00)	15.00 (12.00–18.00)	<0.001[b]
Negative PANSS score	23.00 (19.00–31.00)	17.00 (14.00–21.00)	<0.001[b]	26.00 (21.00–39.00)	18.00 (15.00–26.00)	<0.001[b]
General PANSS score	43.00 (41.00–56.00)	29.00 (26.00–34.00)	<0.001[b]	46.00 (37.00–57.00)	27.00 (23.00–31.00)	<0.001[b]

Median and interquartile range (25th–75th), BDNF, brain-derived neurotrophic factor; ECT, electroconvulsive therapy; PANSS, Positive and Negative Syndrome Scale; PT, pharmacotherapy;
[a]Mann Whitney U test,
[b]Wilcoxon Test. A significance level of $p = 0.05$ was accepted for all analyses.

Baseline versus post-treatment BDNF levels

Mean pre-treatment serum BDNF level was 0.141 ± 0.161 ng/ml in the PT group and 0.320 ± 0.921 ng/ml in the ECT group, while mean post-treatment serum BDNF level was 0.468 ± 1.089 ng/ml in the PT group and 0.315 ± 0.931 ng/ml in the ECT group. The mean BDNF level of the control healthy group was 1.478 ± 1.761 ng/ml (Table 2).

The mean BDNF level of the healthy control group was significantly higher than mean pre- as well as post-treatment BDNF values of both PT and ECT groups ($p < 0.05$ for all comparisons). The post-treatment BDNF levels in PT group were higher than ECT group (Table 2). Additionally, the increase in the mean BDNF levels after treatment in the PT group approached significance ($p = 0.052$), while the difference in the ECT group did not reach statistical significance ($p = 0.632$) (Table 2).

Baseline versus post-treatment PANSS scores

At the end of the study, the mean total PANSS score was 65.16 ± 11.76 (minimum = 49.00, maximum = 92.00) in the ECT group and 63.54 ± 15.63 (minimum = 42.00, maximum = 111.00) in the PT group. These data indicate a significant decrease in total PANSS score and PANSS sub-scores after treatment in both groups (Table 1). Spearman correlation analysis showed no significant correlation between the amount of change in total PANSS scores and the amount of change in serum BDNF levels after treatment in both groups ($p > 0.05$) (Table 3).

The pre-treatment and post-treatment percent change in BDNF levels were calculated. According to multiple linear regression analysis, it was found that previously applied ECT ($p = 0.392$; CI = −463.09 to 184.74), duration of current hospitalisation (days) ($p = 0.540$; CI = −6.68 to 14.81), total duration of previous hospitalisations (days) ($p = 679$; CI = −0.89 to 1.35), total number of ECT sessions applied in the past ($p = 0.728$; CI = −1.42 to 1.00), mean chlorpromazine equivalent dose of the antipsychotic treatment given during hospitalisation (mg/day) ($p = 0.627$, CI: −0.30 to 0.18) and total PANSS scores at the beginning of treatment ($p = 0.363$; CI = −3.17 to 8.33) were not statistically significant factors to predict any pre- and post-treatment change in BDNF levels (Table 4).

Discussion

Dysregulation of BDNF levels can result in symptoms of schizophrenia with various studies showing a lower level of BDNF in schizophrenia patients. As a result, any change in schizophrenia symptoms may coincide with a change in BDNF levels. The aim of the current paper was to evaluate this relationship. In addition, the variations in BDNF levels before and after ECT or PT were investigated and compared to changes in symptom severity. The current study focused only on an acute response to treatment. Results of this study showed that BDNF level was lower in schizophrenia patients relative to healthy controls before PT and ECT. While the BDNF level in the ECT group did not change after treatment, a change in BDNF level was observed in the PT group. Post-treatment BDNF levels were higher in the PT group compared to the ECT group.

Pre-treatment serum BDNF levels were found to be lower in patients with schizophrenia compared to the healthy controls irrespective of whether the patient underwent ECT or PT. A careful evaluation of the recent literature suggests the presence of a consensus on that patients with schizophrenia have relatively lower peripheral BDNF levels compared to healthy individuals. In a meta-analysis of 1144 patients with schizophrenia and 970 healthy controls, peripheral BDNF levels in schizophrenia patients were reported to be lower than the healthy controls (Green *et al.*, 2011). Another meta-analysis including 41 cross-sectional and prospective trials and more than 7,000 participants also found that

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Table 2. Comparison of study groups in terms of BDNF level changes

	Control group (n = 35)	Schizophrenia patients (ECT) (n = 19)		Schizophrenia patients (PT) (n = 35)		*p*								
	(I)	Before ECT (II)	After ECT (III)	Before PT (IV)	After PT (V)									
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	I–II[a]	I–III[a]	I–IV[a]	I–V[a]	II–III[b]	II–IV[a]	III–IV[a]	IV–V[b]
BDNF	1.478 ± 1.761	0.320 ± 0.921	0.315 ± 0.931	0.141 ± 0.161	0.468 ± 1.089	0.892	0.039	<0.001	<0.001	0.632	0.892	0.039	0.052

SD, standard deviation; ECT, electroconvulsive therapy; PT, pharmacotherapy; BDNF, brain-derived neurotrophic factor;
[a]Mann Whitney U analysis,
[b]Wilcoxon analysis. A significance level of $p = 0.05$ was accepted for all analyses.

Table 3. The relationship between the amount of change in PANSS scores and the amount of change in serum BDNF levels

	ECT group		PT group	
	BDNF levels(Δ)		BDNF levels(Δ)	
	r	*p*	*r*	*p*
Total PANSS scores(Δ)	0.029	0.906	−0.16	0.358
Positive PANSS subscale scores(Δ)	0.036	0.883	−0.163	0.351
Negative PANSS subscale scores(Δ)	0.351	0.140	0.022	0.900
General psychopathology PANSS subscale scores(Δ)	−0.092	0.707	−0.251	0.146

Spearman correlation analysis; BDNF, brain-derived neurotrophic factor, ECT, electroconvulsive therapy; PANSS, Positive and Negative Syndrome Scale; PT, pharmacotherapy. A significance level of $p = 0.05$ was accepted for all analyses.

both serum and plasma BDNF levels in patients with schizophrenia were lower than healthy individuals (Fernandes *et al.*, 2015). These findings were confirmed by a number of recent studies (Koeva *et al.*, 2014; Valiente-Gomez *et al.*, 2014; Song *et al.*, 2015; Akyol *et al.*, 2015; Simsek *et al.*, 2015; Chiou & Huang, 2016; Li *et al.*, 2016; Bakirhan *et al.*, 2017; Islam *et al.*, 2017; Li *et al.*, 2018; Weickert *et al.*, 2019). This indicates that the peripheral synthesis of BDNF or its release is reduced during acute schizophrenia episodes, although it is not known whether this is a pathological or countervailing effect.

Results of this study showed that the serum BDNF levels did not improve with ECT; however, a trend-level increase with PT was seen. Although there was no difference in pre-treatment serum BDNF levels between the two patient groups, the serum BDNF levels in the PT group were found to be higher than the ECT group after treatment. A recent study involving 3 groups of patients with 80 patients in the ECT group, 80 patients in the PT group and 77 patients in the healthy control group reported that the post-treatment serum BDNF levels increased in both ECT and PT groups reaching the serum BDNF levels observed in the healthy controls (Li *et al.*, 2016). The results of our study contradict with the results of Li *et al.* in this regard. This difference can be explained in part by the patient selection or sample size. However, to our knowledge, Li *et al.* study is one of the few studies in the published literature that has examined serum BDNF levels after ECT and PT together. Therefore, in order to reach precise deductions to that effect, it is necessary to wait for a more grown data to form consisting of richer results.

Although there is a consensus regarding a lower BDNF levels in patients suffering from acute episode schizophrenia compared to healthy controls, the fate of BDNF after pharmaceutical treatment shows conflicting results. Recent literature suggests the relative success of ECT on non-responders to pharmaceutical therapy in schizophrenia patients (Petrides *et al.*, 2015; Chan *et al.*, 2019). Therefore, at the beginning of the study, we expected the BDNF values to reach higher levels in the ECT group compared to the PT group. Surprisingly, our study showed a lack of difference in pre- and post-treatment serum BDNF levels in the ECT group and this finding does not support the results of Li *et al.* (2016). However, there was a trend-level increase in BDNF levels in the PT group in our sample and post-treatment BDNF levels were significantly higher in the PT group compared to the ECT group. Differences in patient characteristics and indications for ECT

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Table 4. Multiple linear regression analysis of some clinical and psychometric properties on predicting the rate of change in BDNF values

	Unstandardised coefficients		Standardised coefficients			95.0% CI	
	B	SE	Beta	*t*	P	LL	UL
(Constant)	−7.92	386.44		−0.02	0.984	−785.78	769.94
Whether or not ECT was applied in previous studies	−139.17	160.92	−0.17	−0.87	0.392	−463.09	184.74
Duration of current admission (days)	4.07	5.34	0.12	0.76	0.450	−6.68	14.81
Duration of past admissions (days)	0.23	0.56	0.07	0.42	0.679	−0.89	1.35
Number of ECT sessions applied in previous admissions	−0.21	0.60	−0.06	−0.35	0.728	−1.42	1.00
Chlorpromazine equivalent dose of current antipsychotic taken during the study (mg/day)	−0.06	0.12	−0.08	−0.49	0.627	−0.30	0.18
Pre-treatment total PANSS scores	2.61	2.84	0.14	0.92	0.363	−3.17	8.33

BDNF, brain-derived neurotrophic factor; ECT, electroconvulsive therapy; PANSS, Positive and Negative Syndrome Scale; PT, pharmacotherapy; N = 54, $R^2 = 0.09$, F = 0.75, $p = 0.609$, SE, standard error; LL, Lower Limit; UP, uper limit; CI, confidence interval. A significance level of $p = 0.05$ was accepted for all analyses.

may be one way to explain this discrepancy. In the current study, 86% of the patients in the ECT group had referral indications of non-response to other treatments. In line with that, the length of hospital stays and the average daily chlorpromazine equivalent dose in the patients in the ECT group were higher than the PT group. Although there was no difference in pre-treatment disease severity between the two patient groups, the group receiving ECT can be considered as a subgroup with difficulties in treatment. The study by Li *et al.* (2016) did not report the indications that would qualify a patient for ECT which is known to have a diverse range of indications (American Psychiatric Association, 2001). This may have led to the inclusion of patients with different characteristics to the ECT group in the current study, leading to different outcomes compared to Li *et al.* (2016).

A study on treatment-resistant schizophrenia that divided the cases into responders and non-responders to clozapine reported that the serum BDNF levels of clozapine-responsive cases were higher than non-responders (Krivoy *et al.*, 2018). This study, however, did not report a comparison of pre- and post-treatment serum BDNF levels as all serum samples were obtained after 18 weeks of pharmaceutical treatment (Krivoy *et al.*, 2018). One can see that there is a lack of change in serum BDNF levels even with ECT in specific clinical subgroups in our study. We believe that this result may be due to the fact that the BNDF levels of difficult-to-treat schizophrenia patients are more resistant to increase with treatment. Therefore, it is clear that new studies are needed to evaluate BDNF levels before and after PT and ECT in the context of responder and non-responder schizophrenia patients to various treatments.

In the current study, no relation was found between pre- and post-treatment PANSS scores and serum BDNF levels in both ECT and PT groups. In addition, there was no difference in clinical parameters and the relationship of these clinical parameters with serum BDNF levels between the two patient groups, neither before treatment nor after treatment. Various studies have supported (Niitsu *et al.*, 2014; Akyol *et al.*, 2015; Chiou & Huang, 2016; Li *et al.*, 2016; Kudlek-Mikulic *et al.*, 2017; Binford *et al.*, 2018) and not supported (Yamamori *et al.*, 2013; Renjan *et al.*, 2014; Valiente- Gómez *et al.*, 2014; Fernandes *et al.*, 2015; Song *et al.*, 2015; Simsek *et al.*, 2015; Bakirhan *et al.*, 2017; Wu *et al.*, 2018; Weickert *et al.*, 2019) a relationship between peripheral BDNF levels and the severity of positive and negative symptoms that constitute the core phenotype of schizophrenia patients. To our view, a decrease in BDNF levels may cause pathologies at a molecular level before they cause behavioural symptoms. This suggests that a change in BDNF levels may occur before the symptoms appear in schizophrenia patients, which may explain the observations of our study. Thus, while a separation of patients according to clinical subtypes of schizophrenia makes sense from a clinical point of view, it does not mean that this concept would correspond at the neurobiological level. Additionally, differences in genetic polymorphisms of the BDNF gene as well as presence of mature or precursor (pro-BDNF) as the dominant BDNF subtype can be determining factors on how the peripheral or brain tissue BDNF levels react upon various treatment options (Bathina & Das, 2015). Therefore, another explanation for the variations in outcomes of our study may be due to hidden genetic characteristics of the patient sample chosen for the study.

The current study aimed to support data obtained from previous studies carried out in model organisms and to enrich the limited clinical research literature available in this field. Our results reveal that ECT does not increase BDNF levels in schizophrenia patients along with other results. Findings from our study as well as inconsistencies in the outcomes of various studies in the literature suggest that there is a long way to go to before definitive conclusions can be reached. Well-designed studies with large sample sizes are needed to address these inconsistencies and make more precise generalisation on BDNF and schizophrenia relationship.

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Conflict of interest. We as authors of this research paper certify that we have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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Ethical standards. We as authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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