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Electroconvulsive Therapy and Extracellular Matrix Glycoproteins in Patients with Depressive Episodes

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ABSTRACT

Background: The brain extracellular matrix (ECM) is composed of glycoproteins deriving from the cell membrane and joining into nets called perineuronal nets (PNNs). The ECM glycoproteins limit neuroplasticity, cell proliferation, and differentiation. Electroconvulsive therapy (ECT) is provided by electrical currents that may alter several cascades and biophysical effects. ECM conformation might be influenced by the effects of ECT.

Methods: Patients with depressive disorders (n = 23) and healthy control subjects (n = 21) were enrolled. Serum levels of the ECM glycoproteins versican, brevican, neurocan, phosphocan and tenascin C were measured with enzyme-linked immunosorbent assay. Serum samples were collected from the patients in the patient group at 3 time points: before ECT, 30 min after the first session, and 30 min after the seventh session.

Results: There was a significant difference in tenascin C levels (P = .001) between the groups. No other significant difference was observed. Serum levels of the measured ECM glycoproteins and prolidase activity did not differ in the depression group after the administration of ECT.

Conclusions: Our results did not support the claim suggesting a possible mechanism for modulation of ECM glycoproteins by ECT. Serum levels may not necessarily reflect conformational changes in the ECM. Further studies are needed to investigate the effects of ECT on ECM glycoproteins. Modulation of the ECM may provide a new window suggesting improvement in treatments.

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INTRODUCTION

Depression is the most prevalent psychiatric disorder in the community,[1,2] with a lifetime prevalence of 10.8%.[3] The World Health Organization ranks depression as second in the global burden of diseases.[4] Despite the advances in technology and medicine, depression remains a disabling disorder with a chronic course.[5,6] Severe depression may lead to suicide and increased mortality.[7] Treatment resistance is frequent, and almost half of the patients do not respond to adequate treatments properly.[8] In severe cases which are presented with catatonia, acute agitation, nutritional deficiency, psychosis or high suicide risk, ECT remains a lifesaving treatment option.[9,10]

ECT has been used to treat psychiatric disorders for decades. The mechanism of effect of ECT has been extensively investigated. Consistent findings indicate changes in cerebral blood flow, regional metabolism, changes in the blood-brain barrier, neurotransmitters, neuroplasticity, gene expression, epigenetics, and the neuroendocrine, immune, and neurotransmitter systems.[11,12] Classically, seizures are proposed to invoke cytoprotective effects. However, it was later observed that physical effects of the electrical stimulus may also contribute to ECT's therapeutic effects. In line with this, transcranial direct current stimulation or transcranial magnetic stimulation provides therapeutic effects with only electrical stimulation. Studies with these methods suggest that direct influences of electrical currents provide neurotrophic and neuroplasticity effects,[13] which overlap with the effects of ECT.

The direct effects of electrical currents in the brain are suggested to alter membrane polarization dynamics.[14] On the other hand, the intercellular space is a conductive

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compartment for electric currents. Intercellular space is constructed with extracellular matrix (ECM) glycoproteins. ECM glycoproteins establish perineuronal nets (PNNs) by forming chemical bonds between their molecules. The chemical bonds, particularly covalent bonds, might be transiently altered by the electrical currents. Therefore, it is possible that the electrical induction phase of the ECT may cause a transient distortion in the PNN configuration. For example, amyloid beta peptides are transiently increased in the peripheral circulation in 30 min after ECT, and disappear 2 h later.[15] Amyloid beta is a protein laid in the cell membrane and spreads through extracellular space. Therefore, the protein might be fragmented by the electric currents. Another important finding concerns the matrix metalloproteinase (MMP) enzymes, which are involved in the modification of ECM proteins. It has been reported in a study that MMPs were upregulated by ECT application.[16] Collagen degradation is initiated by activation of MMPs, resulting in smaller peptide chains which would be substrates for other peptidases.[17]

The degradation of ECM by the enzymatic activity of MMPs results in the accumulation of imidopeptides with C-terminal proline or hydroxyproline.[18,19] Prolidase is a manganese-dependent cytosolic exopeptidase that plays an important role in ECM remodeling.In addition, prolidase plays a key role in several physiological and other pathological processes such as wound healing, inflammation, angiogenesis, cell proliferation, and carcinogenesis.[18,19] For example, there is evidence showing that nitric oxide[20] and hypoxia-inducible factor-1[21] regulate prolidase gene expression. Prolidase and prolinase are critical enzymes for ECM turnover, and mass collagen breakdown occurs during conditions of metabolic stress.[22]

Organization of the ECM in the brain is highly complex. Proteoglycan molecules form chains and thereby nets covering the surface of the neurons, establishing proteoglycan (PG) sheaths called perineuronal nets (PNNs). Hyaluronic acid (HA) and chondroitin sulfate (CS) are the most abundant carbohydrates establishing molecular chains. Lecticans are the most abundant PGs in the brain, and they bear CS in the ECM. A link protein stabilizes hyaluronan-lectican interactions and the C-terminal domain binds to membrane-associated sulfoglycolipids such as tenascins.[23] The CS chains are large and highly negatively charged, which provides them with a unique structure and function. Neuronal growth and plasticity are controlled by the ECM and much of these effects are due to the presence of the highly negatively charged CS chains. Yet, significant growth inhibition activity is retained after removal of the CS chains, and axonal growth is inhibited by lecticans (Monnier et al. 2003). Consistently, PNNs are looser and flexible in babies, and develop and aggregate with maturity during the developmental period[24]; and lectican expression significantly increases in parallel with aging in the brain.[25] Cognitive dysfunction in advanced age has been shown to be related to ECM abnormalities.[26,27] Furthermore, the ECM that surrounds the synapse may be important in regulating structure and function of the synapse.[28] Modulation of the synaptic ECM is shown to be related with changes in neurotransmission and neuroplasticity.[29] Brevican, aggrecan, versican, and neurocan are a family of proteoglycans (PGs) named lecticans. Typically, lecticans are predominantly expressed by neurons and glial cells. On the other hand, in disease conditions fibroblasts, pericytes, and inflammatory cells may also produce these proteins.[30] Neurocan and brevican are specific to the brain. Full-length neurocan is synthesized during development. In the adult brain, only fragments of neurocan are expressed. However, its full-length expression increases during an injury in the brain.[31]

It was hypothesized in this study that the electrical stimulus of the ECT (induction phase) may distort chemical bonds, particularly covalent bonds (since they are based on electron sharing), and therefore may cause conformational changes in the ECM glycoproteins. Their tertiary and quaternary protein structure may dissociate and the ECM glycoproteins then unfold or probably fragment. Fragments of the proteins would be recycled by lysosomal function in phagocytosis or may pass the brain-blood barrier, and would circulate in the blood until they arrive at the liver for metabolism. The literature regarding ECM abnormalities in psychiatric and neurological disorders has grown substantially. A number of studies have shown ECM abnormalities in schizophrenia,[32,33] bipolar disorder,[34] major depressive disorder,[35] and Alzheimer's disease.[26] Modulation of ECM abnormalities may provide an opportunity to provoke alterations in several cascades and mechanisms,[36,37] opening a new window to the treatment of psychiatric disorders. In this study, we aimed to assess changes in serum levels of neurocan, brevican, versican, phosphocan, and tenascin C in depressive patients who were treated with ECT. Changes in the levels of these proteins may indicate potential effects of ECT on ECM formation and its protein components. Since amyloid beta levels were found to be increased following ECT,[15] it is possible that the same biophysical dynamics may influence the other ECM glycoproteins. In addition, since serum prolidase activity may reflect any potential mass collagen turnover, it was also aimed to assess serum prolidase activity in patients with depression before and after ECT application. In short, the electrical current used in the induction phase of the ECT may cause transient changes in the ECM glycoproteins. Transient changes in the ECM may induce rapid changes in the neuroplasticity cascades by reducing the restrictive control of the ECM over neuroplasticity. This hypothesis may contribute to our understanding about the mechanisms of electrical stimulation therapies.

METHODS

Participants

The study was conducted in compliance with the Declaration of Helsinki. Approval from the local ethical committee was obtained for the study (Approval Date: June 29, 2016, No: 2016/08/14). All participants provided a written informed consent before study enrollment. Consecutive patients with depressive episodes (either patients diagnosed with major depressive disorder or patients with bipolar disorder in depressive episodes) whose treatment was planned with ECT (decisions were made by independent senior physicians) were invited to participate in the study. Patients and healthy control subjects were evaluated according to the inclusion and exclusion criteria. Patients were invited to enroll in the study, and a first-degree relative also approved the participation of the patients. Patients who agreed to participate were enrolled. There were 2 patients who did not agree to participate, and 2 patients who withdrew from the study. Participants were between the ages of 21 and 61. All patients were taking combinations of psychotropic medications (antidepressants, antidepressants + antipsychotics and benzodiazepines). Their usual psychopharmacological therapy was continued during the course of the study. The pharmacotherapy of the patients was not restricted in any way, in accordance with the protocol of this study, and a comparison on the possible effects of the drugs was not included in the design of the study. Medical and psychiatric histories were checked in terms of exclusion criteria. The exclusion criteria were the presence of any medical comorbidities (systemic or neurological diseases), psychiatric comorbidities, history of major surgeries (brain, cardiac, thoracic, or abdominal surgery), any infectious diseases in the preceding month, nutritional deficiencies, and rapid reduction in weight. A total of 23 patients (7 patients with bipolar disorder, 16 patients with major depressive disorder) were enrolled in the depression group. A healthy control group (n = 21) was also recruited. Healthy controls (HCs) were examined with the SCID non-patient form. Exclusion criteria for HCs were history of substance and alcohol-use disorder, cranial injury, major surgery, or any infectious disease in the preceding month.

Clinical Assessment and Measures: Sociodemographic form: A detailed form was prepared by the authors to obtain demographic and clinical variables from the participants. Details of age, gender, education, marital status, and socioeconomic variables were obtained.

SCID-I: Diagnoses were checked with a structured clinical interview for DSM-IV (SCID-I) by a senior psychiatrist.[38,39] The SCID-I is a clinician-administered diagnostic tool to screen for mental disorders (except personality disorders).

Hamilton Depression Rating Scale: Symptom severity was assessed with the Hamilton Depression Rating Scale (HDRS),[40,41] of which 17-, 21-, and 24-item versions are available. The 17-item version was used in this study. The subject was rated by a clinician on a scale of 0-4 points on a Likert-type scale. Symptoms with a rating of over 7 points were classified as indicating depression, and those rated 19 and over were termed as severe depression.

Brief Psychiatric Rating Scale: The Brief Psychiatric Rating Scale (BPRS) was developed by Overall and Gorham[42] in 1962. Depression, anxiety, hallucinations, and symptoms of unusual behavior can be assessed. Each symptom is rated on a scale of 1-7 points, and depending on the version, a total of 18-24 symptoms are scored.

ECT Application

The decision to administer ECT was made by the patients' attending psychiatrists. A written informed consent was obtained from the patient or a first-degree relative before ECT administration. The attending psychiatrist routinely provided information about the procedure, expected benefits, and adverse effects to the patients in the ward, before their first ECT session. ECT sessions were performed in the ECT unit of the hospital between 08.00 AM and noon. ECT procedures of the hospital were all performed in a unit of the hospital that is equipped for anesthesia procedures, as described elsewhere.[43,44] The ECT unit was fully equipped with the devices needed for ECT application under anesthesia and life-support systems such as ventilator, respirator, defibrillator, and electrocardiogram (ECG).[45] According to the routine ECT procedures, all patients were controlled with laboratory tests, including a hemogram, and liver, kidney, and thyroid function tests. Patients were on fasting for 12 h prior to ECT sessions. Blood pressure, ECG, and oxygen saturation were monitored. A pulse oximeter (Nonin 2500A pulse oximeter) placed on the index finger monitored the vital signs. Succinylcholine (0.5 mg/kg) and propofol (0.75-1 mg/kg) were administered as anesthetic medications. Before electrical stimulation, patients had ventilation support with an airway, Ambu mask and bag. During the electrical stimulation and convulsive phase, dental arches were protected with a sponge. A brief-pulse square-wave ECT device (Thymatron System IV ECT; Somatics, Inc., Lake Bluff, IL, USA) was used. ECT applications were bilateral fronto-temporal. Initial electrical stimulus charge energy was set by the doctor according to the half-age criteria and other influencing factors such as concomitant pharmacotherapy, age, and gender, prior to the ECT. Seizures were considered as effective if they lasted more than 25 s. When the electroencephalogram recorded a seizure duration of less than 25, the patients were re-stimulated at a dose increased by 50%, with a maximum of 3 times in a session. In the subsequent sessions, when the duration of convulsions decreased to 25-30 s, the dose was increased by 10%. All

patients were under intense medical care until complete recovery (30–60 min).

Serum Sample Collection and Biochemical Analysis

Blood samples were obtained from antecubital veins, at intervals between 8:00 AM and noon. All participants were controlled to be on 12 h of fasting. Three samples were collected from each patient at different time points: prior to the first ECT session [first] at 8:00 AM, after the first session [second], and after the last session [third]. The second and third serum samples were collected from the antecubital veins in 30-45 min after the ECT administration. The blood samples were left for 30 min at room temperature (22°C) to activate the clotting process, followed by centrifuging at 1500 **g** for 15 min. Serum samples were aliquoted and kept in a freezer at -80°C. Samples were transferred to the laboratory for enzyme-linked immunosorbent assay (ELISA) analyses. Serum levels of tenascin C, neurocan, phosphocan, brevican, and versican were measured with the ELISA method.

Plasma prolidase activity was evaluated with the following method: diluting solution (1 mM $MnCl_2$ in 6 mM Tris-HCl buffer (pH 7.8-8.0)), standard proline solution (650 µmol/L proline solutions in 0.45 mol/L trichloroacetic acid), and glycyl-L-proline solution (94 mmol/L Gly-l-Pro solution in 0.05 mol/L Tris-HCl buffer containing 1 mmol/L of $MnCl_2$ (pH 7.8-8.0)) were prepared. Serums were diluted 40-fold with 2.5 mmol/L Mn^{2+}, and 40 mmol/L trizma HCl buffers (pH 8.0) and were pre-incubated at 37°C for 2 h. The reaction mixtures containing 30 mmol/L Gly-l-Pro, 40 mmol/L trizma HCl buffer (pH 8.0), and 100 µL of preincubation serums in 1 mL were incubated at 37°C for 30 min. The addition of 0.5 mL of 20% trichloroacetic acid solutions then stopped the incubation reactions. Proline molecules in the supernatants were measured as described by Myara et al.[46] Intra-assay concentration of the assay was 3.8%.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM SPSS Corp.; Armonk, NY, USA). The variables were checked with Kolmogorov-Smirnov or Shapiro-Wilks tests for distribution characteristics. Mann-Whitney *U* test or independent samples *t* test was performed for comparison of the 2 groups. Logarithmic transformations were applied for the non-normally distributed variables for further analyses. One-way analysis of variance or Kruskal-Wallis tests were performed for comparison of 3 groups. The first, second, and third samples of the depression group were also compared using the paired samples *t* test. Correlations between the groups were evaluated with Spearman's rank correlation test. All tests were two-tailed, and the level of statistical significance was 0.05.

RESULTS

Sociodemographic Variables

The demographic variables of the groups are presented in Table 1. The groups were similar in terms of gender [$X^2(1, 44) = 0.09$, $P = .763$]. However, age ($t = 2.37$, $P = .022$) and education ($t = -4.49$, $P < .001$) were significantly different between the groups. The participants in the healthy control group were significantly younger than those in the depression group. In addition, the healthy control group had more years of education in comparison to the depression group. The depression scale scores were significantly higher in the depression group compared to the healthy control group. Depression scores significantly reduced after the ECT treatment in the depression group. The patient group had a mean number of 7.14 ± 2.03 sessions of ECT.

Versican, brevican, neurocan, phosphocan, and tenascin C levels and serum prolidase activity were compared between the groups (Table 2). The phosphocan and tenascin variables did not show normal distribution according to the

Table 1. Clinical and Sociodemographic Characteristics of the Participants

	Depression ($n = 23$)	HC ($n = 21$)	t/X^2	P
Gender (women/men)[a]	11/12	11/10	0.09	.763
Age*,[b]	43.04 ± 11.69	35.43 ± 9.34	2.37	**.022**
Education*,[b]	7.09 ± 3.09	12.90 ± 5.31	−4.49	**<.001**
Number of ECT sessions[a]	7.14 ± 2.03			
Duration of the disorder**,[b]	12.46 ± 11.29			
Number of hospitalizations[b]	3.17 ± 3.19			
Number of days in hospital[b]	27.50 ± 9.10			
HDRS—before[b]	35.70 ± 12.10	0.81 ± 1.57	13.10	**<.001**
BPRS—before[b]	30.96 ± 10.68	1.86 ± 2.73	12.12	**<.001**
HDRS—after[b]	11.32 ± 8.59			
BPRS—after[b]	8.91 ± 7.11			

[1]Bipolar disorder depressive episode or major depressive disorder, *years, **months. [a]Means ± standard deviations (*t* test), [b]frequency and percentages (chi-square Test) are reported.

Table 2. Comparison of Serum Lectican Levels and Prolidase Activity Between the Depression and Healthy Control Groups

	Depression (n = 23)	HC (n = 21)	t/Z	P
Versican[a] (pg/mL)	1282.86 ± 624.81	1097.67 ± 572.88	1.02	.318
Brevican[a] (ng/mL)	1.79 ± 1.64	1.04 ± 0.74	3.71	.060
Neurocan[a] (ng/mL)	3.47 ± 2.08	4.18 ± 2.24	1.21	.278
Phosphocan*[,b] (ng/mL)	0.66 (0.47-1.40)	0.58 (0.39-1.18)	−1.05	.296
Tenascin C*[,b] (pg/mL)	460.50 (371.00-887.50)	3659.00 (1255.50-4505.50)	−3.48	**.001**
Prolidase[a,c] (U/L)	442.77 ± 181.43	595.18 ± 72.85	−3.59	**<.001**

[a]*t* test [means ± standard deviations are reported], [b]Mann-Whitney *U* test [median (interquartile range) values are reported], [c]Cohen's $d = 0.96$.

Kolmogorov-Smirnov test ($P < .05$). Tenascin C ($Z = -3.48$, $P < .001$) levels were significantly lower in the depression group than in the healthy control group. No significant difference was observed between the groups in terms of versican, brevican, neurocan and phosphocan levels.

Serum levels of versican, brevican, neurocan, phosphocan and tenascin proteins and serum prolidase activity were compared within the depression group at baseline (before ECT), and after the first and seventh sessions (Table 3). No significant differences were observed between the groups in terms of the measured variables.

Spearman's rank correlation tests were performed with versican, neurocan, brevican, phosphocan, and tenascin C in the depression and healthy control groups. Other variables in the correlation analyses were clinical evaluation tools (CGI, BPRS, and HDRS), body mass index, biochemical indicators (AST, ALT, sodium, potassium, chloride, albumin, total protein, fasting glucose, urea, creatinine, total cholesterol, and triglyceride levels), hormone (thyroid-stimulating hormone and T4), and hemogram (Hb, Htc, Plt, white blood cell, neutrophil, lymphocyte) test results. Accordingly, serum neurocan level had inverse correlation with serum sodium level ($r = -0.38$, $P = .074$) and positive correlations with the BPRS score ($r = 0.67$, $P = .001$) and creatine levels ($r = 0.38$, $P = .086$) in the healthy control group. Versican had correlations with triglyceride levels ($r = 0.46$, $P = .035$) in the depression group, and potassium levels ($r = 0.45$, $P = .039$) in the healthy control group. Brevican had correlations with WBC counts ($r = 0.59$, $P = .004$) and triglyceride levels ($r = 0.61$, $P = .002$) in the depression group. Serum phosphocan level was correlated with serum triglyceride levels ($r = 0.44$, $P = .043$) in the depression group. Tenascin C had correlations with WBC ($r = 0.62$, $P = .003$) and Plt ($r = 0.67$, $P = .001$) counts in the depression group, and age ($r = -0.39$, $P = .079$, trend level) in the healthy control group. Prolidase levels were correlated with serum sodium levels ($r = -0.44$, $P = .035$) and Htc ($r = 0.0.44$, $P = .040$) in the depression group.

DISCUSSION

In this study, extracellular matrix glycoproteins versican, brevican, neurocan, and phosphocan (lecticans) and tenascin C levels were assessed in patients with depression and compared with those in HCs. In the patient group, we had a longitudinal assessment before ECT, and after the first and the seventh sessions. In baseline assessment, there was a statistically significant difference between the groups in terms of tenascin C levels ($P = .001$). The depression group had lower levels of tenascin C, in comparison to the healthy control group. Brevican was higher in the depression group, at trend level ($P = .060$). No other significant difference was observed between the groups. In the longitudinal assessment, levels of the proteins did not differ in time. The initial hypothesis of this study was the claim that electrical current during the ECT induction may distort chemical bonds of the ECM, ECM glycoproteins may become unfolded or even fragmented, and their levels would increase in the serum. This hypothesis is not supported by these findings. However, these findings cannot negate this hypothesis, because of the reasons

Table 3. Comparison Serum Lectican Levels and Prolidase Activity Within the Depression Group

	Before ECT	After First Session	After Last Session	F/X^2	P
Versican[a] (pg/mL)	1282.86 ± 624.81	1261.86 ± 628.81	1334.25 ± 688.82	0.07	.934
Brevican[a] (ng/mL)	1.79 ± 1.64	1.55 ± 1.96	1.22 ± 1.10	0.68	.512
Neurocan[a] (ng/mL)	3.47 ± 2.08	5.14 ± 3.04	5.45 ± 3.66	1.06	.354
Phosphocan*[,b] (ng/mL)	0.66 (0.47-1.40)	0.76 (0.53-0.92)	0.63 (0.38-1.13)	0.81	.666
Tenascin C*[,b] (pg/mL)	460.50 (371.00-887.50)	409.00 (351.00-521.00)	395.00 (321.00-479.00)	2.80	.246
Prolidase[a] (U/L)	442.77 ± 181.43	476.29 ± 168.08	496.02 ± 174.97	0.51	.601

[a]One-way analysis of variance [means ± standard deviations are reported], [b]Kruskal-Wallis test [median (interquartile range) values are reported].

listed below. First, proteins may not become fragmented although their molecular structure is altered. Second, even if they become fragmented, the blood-brain barrier may not let the protein fragments pass to the blood circulation from the brain. Third, amino acid chain fragments of the protein may not be captured by the measurement method. Fourth, fragments of the protein might be eliminated so fast that the protein levels may return to normal states until the time of sample collection. These probabilities might be investigated with further studies. In isolated protein experiments, it is consistently observed that electrical fields and currents alter the structure of the proteins, since they are charged particles.[47,48]

Overproduction of the ECM glycoproteins by the reactive glial cells has been observed in many studies following injury or disease conditions in the brain.[36,49] Increased density of ECM glycoprotein nets limit axonal plasticity, regeneration, remyelination, and conduction of signals.[50] Furthermore, cytoprotection, cell replacement activities such as cell migration, or differentiation are also restricted by excessive inhibitory signals from the ECM glycoproteins. A growing body of literature has shown potential benefits of manipulating ECM glycoprotein nets in combination with other therapeutic strategies for promotion of spinal cord repair and regeneration, as reviewed in Dyck and Karimi-Abdolrezaee.[49] Recent developments have shown that ECM glycoproteins contain several receptor types which may provide therapeutic targets for interventions in alteration of ECM glycoprotein nets.[51-53] Modulation of the ECM is thought to have a therapeutic potential for many neurological diseases including epilepsy, dementia, stroke, and amblyopia.[36] These findings indicate that the ECM glycoproteins may offer a new window with high therapeutic potential for psychiatric disorders. Electrical currents of the neuromodulation therapies such as ECT, transcranial direct current stimulation or transcranial magnetic stimulation may stimulate either biophysical mechanisms or receptors of the ECM. One of the biophysical mechanisms for ECM glycoproteins would be that electrical currents may disrupt covalent chemical bonds and fragment ECM glycoproteins. For example, Zimmerman and colleagues have detected that amyloid beta protein levels increase in serum immediately after the ECT administration.[15] Another recent study also showed that levels of MMPs were increased following ECT.[16] This increase might have led to an increase in prolidase activity. However, prolidase activity did not increase in our study. Serum prolidase activity was found to be higher in patients with major depressive disorder[54] and bipolar disorder.[55] On the contrary, there were no significant differences between depressed patients and HCs in another study.[56] In patients with post-traumatic stress disorder, serum prolidase activity was found to be decreased.[57] In this study, serum prolidase activity was found to be depleted in depressed patients in comparison to the healthy control group. Prolidase is associated with many metabolic cascades including second messenger systems, inflammation, and oxidative stress.[58] Because of the complex interactions, more studies with larger sample sizes are needed for reliable results.

The study has several limitations. As mentioned above, the hypothesis of the study was not confirmed by the results. However, the hypothesis of the study should not be discarded, because the results cannot negate the hypothesis based on the above-mentioned limitations. The small sample size may have led to an inflated risk for type II errors. In addition, a relatively small sample size and differences in medication strategies may also have interfered with the results. On the other hand, working with the ECM in patients is possible with only a few methods. To our knowledge, this is the first study to assess the relationship between the ECT and the ECM glycoproteins.

In summary, this study found that ECT administration did not alter serum levels of lectican glycoproteins or tenascin C. The depression group had significantly lower tenascin C levels and slightly increased brevican levels. Although the initial hypothesis is not supported by the findings, the ECM glycoproteins and PNNs might be a potential target for neuromodulation therapies. Future studies in laboratory conditions may evaluate neuromodulation techniques on ECM structure and fast track improvements in treatments seem to be possible.

Ethics Committee Approval: Ethics committe approval was received from the Bakırkoy Research and Training Hospital for Psychiatry (2016/08/14).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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