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# THE EFFECT OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND PHARMACOTHERAPY ON SERUM PROTEIN S100B IN TREATMENT-RESISTANT DEPRESSION

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***Summary***

***Background:*** *Transcranial magnetic stimulation (TMS) is considered an effective and fast option for treating patients with major depressive disorder. With the increase in treatment options, the determination of biomarkers that predict which treatment will benefit patients the most has been a matter of curiosity for researchers.*

***Subjects and Methods:*** *In this study, we aimed to determine the changes in serum concentrations of S100B, a neurotrophic factor thought to play a role in psychiatric disorders after repetitive TMS (rTMS) and anti-depressant drugs (AD) therapy in patients with major depressive disorder(MDD).In this cohort study, rTMS was applied to the left dorsolateral prefrontal cortex(DLPFC) of drug-resistant MDD patients, while another group of MDD patients was treated with AD for three weeks. Patients were evaluated by psychometric tests and serum S100B concentration at baseline and following intervention. There was also a healthy control group in which patients' S100B values were compared at baseline.*

***Results:*** *There is a population with a total of 48 participants.(16 healthy controls,16 anti-depressant treatment groups, 16 individuals who received rTMS in addition to anti-depressant ) A total of 48 participants completed the study, and the S100B levels of the rTMS group and the anti-depressant drug group were found to be significantly higher than the healthy control group. S100B values, which were higher in the anti-depressant and rTMS groups compared to healthy controls, showed a significant reduction in group time interaction (start and end of treatment).*

***Conclision:*** *rTMS of DLPFC demonstrated an effective complementary treatment for treatment-resistant patients with MDD, especially for patients with relatively high serum S100B concentrations.*

***Keywords:*** *Major depressive disorder, S100B, Transcranial magnetic stimulation, Neuroplasticity, Biomarker in psychiatric disorders.*

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## INTRODUCTION

As the most common cause of disability affecting nearly 16% of the global population, major depressive disorder is attracting increasing attention(Kessler et al.2003). Although different rates have been reported regarding the frequency and prevalence due to differences in research methods, studies agree that major depression is an important cause of morbidity. Major depression is characterized by depressed mood or anhedonia accompanied by thoughts, speech, psychomotor activity and slowing down in physiological functions, as well as thoughts of worthlessness, anergy and pessimism. The introduction of antidepressant drugs (AD) has revolutionized the treatment of mood disorders. However, different classes of AD have been used to treat depressive symptoms. Only 60%–70% of patients with depression respond to antidepressant therapy. Of those who do not respond, 10%–30% exhibit treatment-resistant symptoms coupled with difficulties in social and occupational function, decline of physical health, suicidal thoughts, and increased health care utilization (Al-Harbi 2012). While there is a very high level of evidence regarding the efficacy and mechanism of action of electroconvulsive therapy, there is little evidence for the application of transcranial magnetic stimulation (Sahin et al.2017, Sahin et al. 2021). In a study by Svensson et al., all measures of therapeutic efficacy were numerically lower in the rTMS group compared to the ECT group.The differences were not statistically significant, probably due to the small sample size. Further studies are needed in terms of the effectiveness of rTMS (Svensson et al. 2018).

Transcranial magnetic stimulation (TMS) was introduced in 1985 as a technique to stimulate the cerebral cortex non-invasively.A TMS device generates a strong magnetic field, inducing an electric current in a specific area, which in turn induces intracerebral currents in associated neural circuits (Cusin & Dougherty 2012). An electric field will depolarize cortical neurons, creating action potentials.For example, TMS over the left motor cortex causes action potentials that propagate along the corticospinal pathway, causing twitches in the contralateral skeletal muscles (Gershon et al. 2003). Observations on TMS has been conducted on improve depressive symptoms(McConnell et al. 2001). Since then, TMS has been a promising tool with proven efficacy for the treatment of depression, including in patients refractory to antidepressant pharmacotherapy.For patients who do not respond to an antidepressant or experience intolerable side effects, TMS can be a good alternative that is both well tolerated and effective (Liston et al. 2014).

With the increase in treatment options, the determination of biomarkers that predict which treatment will benefit patients the most has been a matter of curiosity for researchers. Studies have shown that different peptides increase and decrease with depression treatment. S100B is a biological marker for neuropathology and neuroplasticity, with altered serum and cerebro-spinal fluid (CSF) levels in many psychiatric diseases, and may be useful for determining treatment efficacy. S100B level in adult patients with depression is considered as a marker of response to treatment (Bilginer et al.2021).Various studies have reported that depressed patients have increased S100B levels in serum and CSF (Rothermundt et al. 2001a, Arolt et al. 2003,Rothermundt et al. 2001b, Schroeter et al. 2002).

The family of S100 calcium-binding proteins modulates cellular responses in calcium dependent signal. S100B is a member of the S100 family(Rothermundt et al. 2003). S100B, one of the proteins involved in neuroplasticity, is found in the human glial cells(Steiner et al. 2007).S100B acts as a neuronal survival protein ın the developing brain and following acute glial activation in response to injury (Van Eldik & Wainwright 2003). This peptide acts as a trophic factor for serotonergic neurons. S100B is involved in the modulation of metabolism and differentiation of neurons and glial cells in brain cells (Šakić et al. 2016).Since it is a small protein (21 kDa in dimeric form), it easily crosses the blood-brain barrier (BBB) (Reiber 2001). S100B is a neurotrophic factor that plays a role in neuroplasticity, and neuroplasticity is impaired in depression; however, treatment with antidepressants may restore neuroplasticity.In previous research, the role of S100B in the antidepressant response was investigated in various trials. Although there was no significant difference in S100B levels before and after AD use, those who responded to antidepressant treatment had significantly higher initial serum S100B levels than those who did not (Jang et al. 2008). In the light of this study, it can be deduced that elevated S100B increases neuroplasticity and is associated with a good response to treatment.

## SUBJECTS AND METHODS

### Study Design

A total of 32 subjects and 16 healthy controls who were diagnosed with major depressive disorder and planned to be treated for AD (16 individuals) and rTMS (16 individuals in addition to AD) were included in this cohort study. We evaluated S100B protein concentrations in MDD patients and healthy controls. We evaluated changes in serum S100B protein concentrations and depression scores in 2 groups receiving rTMS and AD treatment. We identified 3 participant groups. Group 1 (rTMS group) consisted of 16 subjects with treatment-resistant depression (defined as less than a 25% reduction in HAM-D scores in response to adequate doses of one SSRI and the other from the SNRI group for at least 6 weeks. (Rapaport et al. 2006, Berlim & Turecki 2007)). In the rTMS group (diagnosed with MDD in the last 6 months), there was no adequate response to the use of SSRI (sertraline) for at least 6 weeks and SNRI (venlafaxine) for at least 6 weeks. In the final state, 8 patients were using SSRI (sertraline) and 8 patients were using SNRI (venlafaxine). The second group consisted of 16 patients diagnosed with MDD for the first time. SSRI (sertraline) was started in 8 patients and SNRI (venlafaxine) was started in 8 patients. All depressive patients were diagnosed with MDD within the last 6 months and had not received ECT and psychotherapy. Depressive patients did not have a history of suicide. The third group was a group of 16 healthy volunteers.The participants in all 3 groups did not have any autoimmune and chronic diseases. The patients in the rTMS group were using AD.Treatment-resistant depression group received rTMS therapy in addition to AD therapy for 3 weeks (15 sessions in total, 5 sessions per week). The other depression group received AD treatment for 3 weeks.

During the treatment phase, rTMS sessions were scheduled daily in a 5-day sequence, for a 3 weeks (5 sessions per week), and typically administered on a Monday through Friday Schedule. Motor threshold measurements were made before the first rTMS session.In these measurements, the motor threshold value was determined by stimulating the right abductor Pollicis Brevis (APB)

muscle over the left motor cortex. 120% of the detected motor threshold was determined as the application severity of the treatment. In all patients, applications were performed at a frequency of 10 Hz (Stimulation is given below 1 Hz in low frequency TMS and 1 Hz or more in high frequency TMS. The 10 Hz used in our study is high frequency.), The train(s) consist of 40 pulses: 10 pulses a second for a total of 4 seconds, followed by a break of 11.0 seconds.This is repeated 75 times. The total duration is 18 minutes 26 seconds, and the total number of pulses is 3000. The "5 cm rule" was taken as the basis for the coil settlement. Accordingly, 5 cm anterior side on the parasagittal plane from the motor cortex point where the motor threshold was determined was accepted as the application site.This area corresponds to the DLPFC (Dorsolateral prefrontal cortex). The first clinical investigations of rTMS for depression identified the DLPFC target site as being 5 cm anterior to the motor cortical hotspot, overlying Brodmann area (BA) 46 and BA 9 in the Talairach atlas (George et al.1995, Pascual-Leone et al. 1996). This 5-cm method was subsequently used in larger clinical trials that led to Food and Drug Administration approval (Cash et al. 2021). The 5- to 6-cm approach has been the most commonly employed targeting method, accounting for 84% of randomized clinical trials as of 2016 (5 cm: 75%; 6 cm: 9%) (Cash et al. 2021).

There are also alternative approaches to DLPFC goal setting.In a study,neuronavigation enables the TMS coil to be positioned to target specific anatomical sites basedon an individual subject's structural brain images. Both the neuronavigated and the conventional 5-cm approaches yielded reductions in depression severity; however, there was no significant interaction between targeting approach and clinical trajectory across the two cohorts, nor was there clear decrease in response variability across individuals (Cash et al. 2021, Fitzgerald et al.2009).Alternative approaches to DLPFC target identification have been reviewed in the literature, including standardized electroencephalogram electrode positions, various anatomical magnetic resonance imaging (MRI) coordinates focusing around Brodmann areas (BA) 9 and 46, and individualized hypometabolic foci. As a result, these alternative targeting strategies did not lead to significant clinical improvements beyond the 5 cm approach (Fox et al. 2012).

After the prefrontal cortex was determined as the application site, the coil was placed on the scalp at an angle of 45 degrees to the sagittal line.Each session lasted an average of 18 minutes. Evaluation of the data was done with improvement in blood values and depression scores. Therefore, after the 15th TMS session, the data were evaluated together in terms of temporal correlation.In addition, evaluations were made at the end of the 3rd week against the risk of discontinuing the treatment with clinical improvement.In the following period, the protocol of the patients was completed in 20 sessions. Serum S100 B concentration and psychometric tests in both patient groups were compared with those at baseline and 3 weeks after the intervention. Healthy volunteers completed the same screening and baseline assessments as patient groups.

## Participantsand Eligibility Criteria

The study protocol was approved by the local ethics committee of the Gaziantep University Faculty of Medicine (approval number:14.07.2021-2021/157), and the study was performed in accordance with the ethical standards of the Declaration of Helsinki. All the participants provided written informed consentprior to participation in the present study. For all participants, the following inclusion criteria applied: age 18–65 years; able to give informed consent; able to fast for 8 hour and abstain from strenuous exercise for 72 hour prior to venous blood sampling. The following exclusion criteria applied: pregnancy or breast feeding, alcohol or substance use disorder in the preceding 12 months, history of any inflammatory disease or febrile illness 4 weeks before the blood sampling or current use of any medication (e.g. statins, corticosteroids, antihistamines, anti-inflammatory medications).

We recruited three groups of participants, those with treatment-resistant depression, untreated depression and healthy volunteers.Patients were assigned to one of two subgroups,per protocol: Group 1 treatment-resistant depression patient with major depressive episode; the second group is the group in which AD will be started with the diagnosis of major depression. A group of healthy volunteers were included in the study with no history of any major psychiatric disorder as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and no history of AD treatment for any indication.

Adult patients meeting DSM-5 criteria for MDD were recruited from outpatient service of mental health clinic.

## Questionnaire assessments

Diagnosis of MDD and other psychiatric disorders was ascertained by the Structured Clinical Interview for DSM-5.

Current depressive symptom severity was defined by total scores from the 17-item Hamilton Rating Scale for Depression (HAM-D)(Hamilton 1960).

Age, gender, medical history, smoking status and family history were documented by semi-structured clinical interviews.

### Magnetic Stimulation

rTMS application was performed with NEUROSOFT (Russia)-NEURO MS/D brand/model device and a 'figure 8 coil' type coil. During rTMS, 120% of the detected motor threshold was determined as the application severity of the treatment. Left dorsolateral prefrontal cortex (DLPFC) was stimulated.The train(s) consist of 40 pulses: 10 pulses a second for a total of 4 seconds, followed by a break of 11.0 seconds. This is repeated 75 times. The total duration is 18 minutes 26 seconds, and the total number of pulses is 3000. Each treatment session lasted an average of 18 minutes per day for 3 weeks (15 sessions). At the end of the 3rd week, evaluations were made with blood and depression scale scores. Then the number of TMS sessions was completed as 20.

### Serum S100B Measurement

Routine medical evaluation and laboratory examinations (complete blood count, kidney and liver function tests, and urine examination) were performed on all participants. Commercial enzyme-linked immunosorbent measurement (ELISA) reagents for serum S100B level were studied in Gaziantep University Medical Faculty Hospital Biochemistry Department Laboratories. (Used S100b ELISA kit is brand Cloud Clone (USCNK)) Blood samples have been obtained on the 1st and 21st days from patient groups who were initiated rTMS or (and) AD therapy and once from healthy control group. The samples were collected after 8 hours of fasting, blood samples were taken 5 mL into the SST biochemistry tube and kept at room temperature for 20 minutes. After coagulation, the samples were separated into the Eppendorf tube and stored at -80 °C until the working day.

### Statistical Analysis

The conformity of the numerical variables to the normal distribution was tested with the Shapiro Wilk test. The ANOVA test was used to compare the normally distributed variables in three groups (TMS, AD treatment, healthy volunteers).Two-way repeated measures analysis of variance was applied to test normally distributed variables in different groups and times. Relationships between categorical variables (sex,drugs use),were tested with Chi-square test.SPSS 22.0 Windows version package program was used in the analysis. P<0.05 was considered significant.

## RESULTS

All 3 groups formed are homogeneous in terms of demographic and absence of autoimmune and comorbid diseases. A total of 48 participants, 32 of whom had MDD and 16 healthy controls have been enrolled in this study. 48 participants were between the ages of 18-65, with a mean age of 34.85 ± 10.98.rTMS group, 68.8% (n=11) were female and 31.3% (n=5) were male. AD group, 50% (n=8) were female and 50% (n=8) were male.In healthy controls, 43.8% (n=7) were female and 56.3% (n=9) were male. There was no significant difference between the groups in terms of gender (Table 1) (p=0.336).

**Table 1:** Gender demographics of the study population

| | | rTMS applied treatment--resistant depression group | AD applied untreated depression group | Healthycontrol group | |
|---|---|---|---|---|---|
| | | n(%) | n(%) | n(%) | P |
| Gender | Female | 11 (68,8 ) | 8 (50 ) | 7 (43,8 ) | 0,336 |
| | Male | 5 (31,3 ) | 8 (50 ) | 9 (56,3 ) | |

* Significant at the p<0.05 level, Chi-square test

**Table 2:** Serum S100B concentrations by groups before intervening in treatment

| Variables | Depressed Patients (n=32) | Control (n=16) | P |
|---|---|---|---|
| S100B | 344,40 ± 110,98 | 141,96 ± 89,66 | 0,001* |

* Significant at the p<0.05 level
†Student t test

**Table 3:**Changes in serum S100B concentrationsby groups with the treatment process

| | **Baseline measurement of S100B** | **21.day measurement of S100B** | |
|---|---|---|---|
| | Mean±SD | Mean±SD | P |
| rTMS applied treatment-resistant depression group | 366,75± 124,01 | 259,96± 68,72 | 0,106 |
| AD applied untreated depression group | 322,05 ± 94,91 | 231,23± 52,15 | |
| P | 0,001* | | 0,726† |

*Significant at the p<0.05 level, Two-way repeated measures analysis of variance
†treatment groups and time interaction

**Table 4:** Changes in HAM-D scores by groups with the treatment process

| | **Baselinescores of HAM-D** | **21.day scoresof HAM-D** | |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| rTMS applied treatment-resistant depression group | 19,81±2,25 | 11,06±2,88 | 0.03* |
| AD applied untreated depression group | 21,68±3,78 | 15,18±2,40 | |
| P | 0,001* | | 0,012† |

*Significant at the p<0.05 level, Two-way repeated measures analysis of variance
†treatment groups and time interaction

Selective serotonin reuptake inhibitor (sertraline) were started in 8 patients in the AD group, serotonin noradrenaline reuptake inhibitor (venlafaxine) were started in 8 patients, and rTMS was started in cases of treatment-resistant depression. In rTMS group, 8 patients were using selective serotonin reuptake inhibitör (sertraline). Eight patients were using serotonin noradrenaline reuptake inhibitör (venlaxine).

The mean serum S100B concentration in depressive participants was 344.40 ± 110.98 (pg/mL)in depressed patient group and 141.96 ± 89.66 in healthy controls. It was found to be significantly higher in the patient group compared to the healthy controls. There was no a statistically significant baseline difference in S100B levels between the rTMS group and AD group. (Table 2) (P = 0.001)

S100B value decreased from 366.75 ± 124.01 to 259.96 ± 68.72 in the rTMS group and decreased from 322.05 ± 94.91 to 231.23 ± 52.15 in the group receiving AD. There was no significant difference between the groups in terms of S100B values and in the group time interaction (p=0.106, p=0.726), a significant decrease was found in the later measurements compared to the first measurements (p=0.001) (Table 3).

HAM-D values decreased from 19.81 ± 2.25 to 11.06 ± 2.88 in the rTMS group and from 21.68 ± 3.78 to 15.18 ± 2.40 in the AD group.A significant difference was found between the groups in terms of HAM-D values and in the group-time interaction (p=0.03, p=0.012).A greater decrease was observed in the group in which rTMS was started in addition to AD therapy, compared to the group that were only receiving medication. A significant decrease was found in the after measurements compared to the baseline measurements.(p=0,001) (Table 4)

## DISCUSSION

In this study, the researchers observed the changes in serum concentrations of S100B, a neurotrophic factor thought to play a role in psychiatric diseases, among the healthy control group and the patient groups receiving AD or complementary rTMS therapy and they examined whether the serum concentration of S100B is useful as a determinant in the selection of treatment modalities. This study is important because it is one of the rare studies that reveal the change of S100B serum concentration with rTMS therapy.

In the literature, serum concentrations of S100B were found to be significantly higher in the depressed group than in the healthy controls (Arora et al. 2019). In our study, in accordance with the literature, the mean serum S100B concentration of our participants' samples was found to be significantly higher in the depressive patient groups than in the healthy controls. This may indicate that serum S100B concentration can be used as a biomarker in psychiatric disorders in the near future.S100B is thought to be a prerequisite for the neuroplastic changes required to ameliorate depression. S100B is important in neurogenesis as a compensatory response to any impairment in neuroplasticity. Antidepressants exert their effects by increasing neurogenesis and modulating signaling pathways involved in neuroplasticity. In this way, neuroplasticity levels in depressed patients may affect responses to antidepressants(Jang et al. 2008). In this study, treatment-resistant depression group received rTMS therapy in addition to AD therapy for 3 weeks and untreated depression group received AD therapy for 3 weeks and as a result it was determined that the serum concentration of S100B decreased significantly among the baseline to third week measurements. This is consistent with other literature studies showing that the serum concentration of S100B decreases with antidepressant therapy (Schroeter et al. 2002).

In this study, no significant difference was found in the decrease of S100B serum concentration between the patient groups receiving AD and rTMS treatment. While there was a diagnosis of treatment-resistant depression in the patient group selected for rTMS treatment, the significant decrease in HAM-D scores and serum S100B concentrations in both groups is remarkable. It reinforces the idea that rTMS could be an alternative treatment for drug-resistant depression.

A study in the literature also showed that patients with higher baseline serum S100B concentrations responded better to treatment. This may indicate that the basal serum S100B level is associated with increased growth and differentiation of neurons, resulting in a favorable therapeutic response to antidepressants. In addition, patients with elevated baseline serum S100B levels had clinically significant improvement within 6 weeks of treatment with antidepressants. Also, patients with low serum S100B concentration at baseline did not show clinical improvement within 6 weeks of treatment with antidepressants (Jang et al. 2008). In a study conducted in 2015, patients with higher baseline S100B concentration improved more than those with initially lower S100B concentration. Particularly unresponsive individuals can be distinguished with low S100B levels and high sensitivity.S100B can be used as a trait marker for neural plasticity for acute depressive episodes (Ambrée et al. 2015).

In a study conducted in 2013, S100B concentrations were measured before and after the study by applying 3-week rTMS and 3-week sham TMS in patients diagnosed with MDD. In the study, no significant difference was observed in the rTMS group or the sham TMS group before and after the application. Researchers emphasized that this situation could also show that S100B, which was used as a marker for neuron damage, did not cause damage to neurons. However, researchers emphasized that the small sample size (22 depressed patients*)* in the study would increase the possibility of error (Ullrich et al.2013).

The most important limitation of the study is that we could not demonstrate the change in S100B concentrations with only TMS therapy in patients diagnosed with treatment-resistant depression without AD therapy. This was due to the fact that the researchers did not find it appropriate to follow patients diagnosed with treatment-resistant depression without taking medication, due to ethical concerns. Another limitation of our study is, Evaluation of the data was done at the end of 3 weeks, as in some studies in the literature. Evaluations were made at the end of the 3rd week against the risk of discontinuing the treatment with clinical improvement. In the following period, the protocol of the patients was completed in 20 sessions.

## CONCLUSION

S100B concentrations are significantly higher in patients with major depressive disorder than in the control group.Therefore, serum S100B concentrations may be a biological marker in the diagnosis and monitoring of depression in the coming years. There was a decrease in serum S100B concentrations for both groups. In the present study, rTMS of DLPFC demonstrated an effective complementary treatment for treatment-resistant patients with MDD, especially for patients with relatively high serum S100 B concentrations**.** We think that serum S100B concentrations can be an important predictor in the selection of alternative treatment modalities in patients with treatment-resistant depression.

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***Authors contributions:*** Gulcin Elboga: research idea, literatür research, manuscript supervision. Bahadır Demir: research idea, manuscript writing. Ufuk Gonultas : manuscript writing, interpretation of data. Sengul KocamerSahin :research idea, study design. IremSurme: literatüre search, manuscript writing. Abdurrahman Altindag: manuscript revising, manuscript supervision. Seyithan Taysi: Lab work and biochemical analysis

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