

Neurotrophic Factor Levels and Cognitive Functions before and after the Repetitive Transcranial Magnetic Stimulation in Treatment Resistant Depression

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ABSTRACT

Objective: To determine relationship between the therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) on cognitive impairment and brain derived neurotrophic factor (BDNF), glial cell derived neurotrophic factor (GDNF) levels in treatment resistant depression (TRD).

Study Design: Descriptive study.

Place and Duration of Study: Psychiatry Clinic of Konya Beyhekim Training and Research Hospital in Turkey, between June and November 2019.

Methodology: The study included 33 TRD patients and 33 healthy subjects. Patients received a total of 20 sessions of rTMS treatment. Serum BDNF and GDNF levels were measured before and after rTMS treatment. Additionally, the severity of depression as well as cognitive functions were assessed at the baseline and after the treatment.

Results: The rTMS treatment significantly improved depressive and cognitive symptoms in patients with TRD. Although the level of serum BDNF and GDNF increased after rTMS treatment, it was associated with the improvement in symptoms, but not significantly.

Conclusions: rTMS treatment contributes to the antidepressant effect by normalising serum BDNF and GDNF levels in patients with TRD. Adding rTMS to antidepressants is, therefore, an appropriate treatment option for depressive patients with cognitive impairment.

Key Words: rTMS, BDNF, GDNF, Cognitive function.

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INTRODUCTION

A significant percentage of major depressive disorder (MDD) patients exhibit resistance to all available standard treatments. Treatment options for resistant patients includes combining, augmenting or switching medications, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or other neurostimulation strategies. rTMS is a safe, non-invasive neuro-stimulation technique that enhances neuronal plasticity via the modulation of cortical excitability.¹ However, the biological mechanisms of rTMS are still unclear.

The current literature supports the idea of a close relationship between depression and neurotrophic factors.² It is well-known that BDNF levels are reduced in depression and can increase with clinical improvement.³ Changes in GDNF levels have also been reported in depressive patients.^{4,5}

It is reported that the efficacy of antidepressants are reliant on the expression of BDNF and improvement of neuronal plasticity.⁶ Data on the effects of rTMS on BDNF levels are inconsistent. It has indicated that rTMS increases serum BDNF levels⁷ while Tong *et al.* has shown no effect on serum BDNF levels.⁸ A limited number of trials have investigated the effects of pharmacological and non-pharmacological treatments on GDNF levels. ECT was shown to increase serum GDNF levels in patients with TRD.⁹ However, studies focusing on the effects of rTMS on GDNF levels in patients with TRD are lacking.

Several studies have shown that cognitive deficits are present in a wide range of cognitive domains in depression. rTMS has been suggested to improve cognitive symptoms in TRD.¹⁰ Addi-

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tionally, rTMS treatment may increase the serum levels of BDNF in patients with depression. The relationship between the therapeutic effect of rTMS on cognitive impairment and BDNF, GDNF levels in TRD has not been examined enough. Therefore, the aim of the present study was to determine the serum BDNF, GDNF levels and cognitive functions before and after rTMS treatment in patients with TRD.

METHODOLOGY

This descriptive study included 33 patients with TRD, who were consecutively admitted for rTMS between June and November 2019. The present study was approved by the Ethics Committee of the Faculty of Medicine, Karatay University (No: 41901325-050.99). Written voluntary informed consent was obtained from all participants. The inclusion criteria for the depressed patients were age between 18-65 years; diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), treatment resistance, without showing clinical remission after at least two different antidepressant lines at an effective dosage over a period of four weeks during the current depressive episode,¹¹ and HDRS score of at least 18. Exclusion criteria for the MDD patients were comorbid psychiatric disorders, mental retardation, substance use disorder (except smoking), presence of medical diseases (e.g., neurological disorders, cardiovascular and pulmonary system diseases, hepatic and renal failure, cancer, chronic infections), having received ECT and/or rTMS within six months, presence of an implant/pacemaker in the body, and being pregnant or breastfeeding. Thirty-three healthy controls were also included, who had no history of psychiatric, neurological or medical disorders and no history of substance use disorders (except smoking) as confirmed, using available medical records and through interviewing.

A semi-structured interview form developed by the investigating psychiatrists was used to collect data on the socio-demographic and clinical characteristics of the patients and controls. DSM-5 was used for the diagnosis of MDD or other psychiatric disorders. The severity and level of depressive symptoms were assessed with the Clinical Global Impression Scale (CGI),¹² and Hamilton Depression Rating Scale (HDRS).¹³ To evaluate the cognitive functions of the participants, Stroop Test TBAG version was used.¹⁴

Stroop test TBAG form represents a version combination of the original Stroop test and the Victoria Version. The test was employed to measure the severity of attention deficit and executive functions such as cognitive flexibility and suppression. The Stroop test TBAG form comprises of five subtests, using four cards. The increasing number of total errors and corrections and/or total completion duration indicate more severe attention deficit and more impairment of cognitive functions. Its validity and reliability for the Turkish population was provided by Karakaş *et al.*¹⁴

The DSM-5 based diagnosis of TRD was established by a psychiatrist with at least four years of experience in psychiatric disor-

ders and the use of diagnostic instruments. The participants underwent physical examination and biochemical laboratory analyses. The first psychiatric evaluation was performed before rTMS treatment. All patients continued their medication at stable doses. During the first interview, the patients were administered the CGI, HDRS, and Stroop Test TBAG version. The second interview was completed after 20 sessions of rTMS treatment and the same instruments were administered by the same psychiatrist to the patients.

Serum BDNF and GDNF levels were measured in patients before and after rTMS and control groups only one. For each participant, 10 ml peripheral venous blood samples were collected in tubes between 8.00 am and 11.00 am in the fasting state. The blood samples were immediately centrifuged at 3000 rpm for 10 mins for serum separation. Serum samples were stored at -80°C for further analysis.

Human BDNF ELISA kit (Cat. No: SEA011Mi, detection range: 31.2-2,000 pg/mL, Intra-Assay: CV <10%, Inter-Assay: CV <12%, USCN, Life Cloud-Clone Corp. Wuhan, China) was used to measure serum BDNF level by a double antibody sandwich ELISA method in accordance with the manufacturer's directions. An Awareness STAT FAX 2600 microplate washer (Awareness Technology, USA) was used for the washing steps of the ELISA kits. In spectrophotometric measurements, BDNF results were calculated in ng/ml, according to the absorbance-concentration calibration charts, using a microplate absorbance reader Awareness CHROMATE 4300 (Awareness Technology, USA) system.

Human GDNF ELISA (Cat.No: SEA043Hu, detection range: 0.156-10 ng/mL, Intra-Assay: CV <10%, Inter-Assay: CV <12%, USCN, Life, Cloud-Clone Corp. Wuhan, China) kit was used to measure serum GDNF levels with a double antibody sandwich ELISA method in accordance with the manufacturer's directions. An Alisei Next Level microplate washer (Alisei, Italy) was used in the washing steps of these ELISA kits. The GDNF levels were calculated in pg/ml according to the absorbance-concentration calibration charts using the Alisei Next Level microplate absorbance reader (Alisei, Italy) system.

A Neurosoft brand Neuro-MS/D magnetic stimulator device was used in the current study. Patients received a total of 20 sessions of rTMS treatment (five days a week for four weeks). First, the right hand coped with the single beats given to the left motor cortex at the vertex level by means of an 8-shaped coil, and the motor threshold was determined by observing the motion of the abductor pollicis brevis muscle, then fixed on the coil DLPFC with the 5-centimeter technique (advancing 5 cm from the motor cortex in the rostral direction). In this protocol, the 20 Hz stimulation with duration of 2 s was delivered 20 times at 30 s intervals and approximately 100% of the motor threshold in the amplitude. A total of 1000 pulses were applied.

Data analyses were performed with the Statistical Package for Social Sciences (SPSS), version 20.0, for Windows (SPSS Inc. Chicago, IL). One-sample Kolmogorov-Smirnov test was used to analyse the distribution of continuous variables. Moreover, t-

test was used for the comparison of normally distributed continuous variables, while the Mann-Whitney U-test was used for with non-normal distribution between the independent groups. The scores of CGI, HDRS, Stroop test TBAG version, and levels of BDNF, GDNF before and after rTMS treatment were compared with paired t-test or Wilcoxon signed rank test for dependent groups. Pearson product-moment correlation and Spearman's rank correlation analyses were used for the analysis of normally and non-normally distributed parametric variables, respectively. P value below 0.05 was considered significant.

RESULTS

Thirty-three patients with TRD and 33 healthy controls were included in the study. Twenty-two (66.7%) of 33 patients and 21 (63.6%) of 33 controls were females ($p=0.796$). Mean age of patients and controls were 45.21 ± 8.32 years and 44.21 ± 8.46 years, respectively ($p=0.630$). Marital and educational status were similar in patient and control groups (p values = 0.682 and 0.767 respectively). The response rate was 74%, while the remission rate was 50% at the 4th week of treatment.

Before rTMS treatment, serum BDNF and GDNF levels were significantly lower in depressive patients compared to the controls ($p=0.022$ and $p=0.003$, respectively). BDNF and GDNF levels increased after rTMS treatment. HDRS and CGI scores were significantly decreased following rTMS treatment ($p < 0.001$, Table I).

The Stroop scores before and after the rTMS treatment are shown in Table II. The Stroop test reading times decreased in the patients after rTMS treatment. Reducing of reading times for Stroop 1, 3, 4 and 5 (among before and after) were significant. (p values = 0.001, 0.002, 0.001 and < 0.001 respectively).

The GDNF levels were negatively correlated with the HDRS ($r = -0.436$, $p = 0.011$) before rTMS treatment. BDNF levels and GDNF levels were negatively correlated after rTMS treatment ($r = -0.376$, $p = 0.031$).

DISCUSSION

In the study, rTMS led to improvements in depressive and cognitive symptoms in patients with TRD. Serum BDNF and GDNF levels increased after rTMS treatment; however, the serum BDNF and GDNF levels were not significantly correlated with the improvement in disease symptoms.

BDNF plays an important role in neuronal growth and survival, serves as a neuromodulator and contributes to neuronal plasticity, all of which are associated with MDD. In the current study, before rTMS treatment, serum BDNF levels, were found to be significantly lower in the patients compared to the control group. Findings from a systematic review showed that serum levels of mature and pro-BDNF levels were significantly lower in patients with MDD compared to healthy controls.³ Taken together, these findings suggest that abnormalities in BDNF levels are associated with the pathophysiology of depression.

However, studies on the effect of rTMS on BDNF levels in depres-

sive patients have shown inconsistent results. Tong *et al.* administered 20 sessions of rTMS to 60 depressive patients and reported no change in BDNF levels, while Zhao *et al.* has indicated that BDNF level increased significantly after rTMS treatment.^{7,8} In the current study, serum BDNF levels showed an increase after rTMS treatment; post-treatment BDNF levels were statistically similar between patients and controls. These findings corroborate data from published studies suggesting that serum BDNF levels are increased as a result of rTMS treatment.

Changes in GDNF levels have been reported in patients with depression. Diniz *et al.*⁴ reported that GDNF levels were significantly reduced in elderly patients with depression compared to a control group. Similar results were reported in other studies as well.^{5,15} In the current study, it was found that GDNF levels were significantly lower in patients with TRD compared to healthy controls. It was think that the decrease in GDNF level observed in the current study provides additional evidence that GDNF homeostasis may play an important role in the pathophysiology of depression.

It was observed that rTMS treatment increased serum GDNF levels. In addition, post-treatment levels of GDNF in the patients were significantly higher than the control group. A limited number of trials have investigated the effects of pharmacological and non-pharmacological treatments on GDNF levels. Zhang *et al.* reported that serum GDNF levels were increased with antidepressant treatment,¹⁶ suggesting that GDNF can contribute to the recovery of depression. It is also reported that GDNF levels showed an increase after ECT in 16 patients with TRD, particularly in responsive patients.⁹ To the best of authors' knowledge, the current study is the first to report differences in serum GDNF levels in patients with TRD after rTMS treatment.

In a meta-analysis by Xu *et al.*, it was found that rTMS was effective in certain cognitive areas such as memory, executive function, attention, and verbal fluency.¹⁷ Studies have shown that rTMS strengthens the bond between frontoparietal networks after DLPFC stimulation, whereby memory functions and other cognitive functions are improved.^{18,19} Additionally, it is reported that rTMS applied to left DLPFC increases overall performance in the Stroop test in healthy individuals as well as in patients with depression and cognitive impairment.¹⁹ For the mechanism of rTMS related cognitive improvement in the treatment of depression, it is considered probably related to brain behaviour modulation, induction of neuroplasticity, and the prioritizing of functional neurons. Additionally, the therapeutic effects of rTMS on depressive symptoms and cognitive function may be mediated by treatment effects thought to result from neurochemical and blood flow changes within the left DLPFC-cingulate cortex, which has been shown to mediate Stroop task performance in patients.²⁰ The authors suggest that addition of rTMS to pharmacological treatment may not only improve depression symptoms, but may also contribute to cognitive recovery by engaging different neural networks.

Table I: BDNF, GDNF and clinical scale scores before and after rTMS.

	Before rTMS Mean±SD/median, IQR	After rTMS Mean±SD/median, IQR	Control Mean±SD/median, IQR	P1	P2	P3
HDRS	10.00 ^c , 26 ^d	6.45±3.43 / 3.00 ^c , 5 ^d	1.48±1.17	<0.001 ^a	<0.001 ^b	<0.001 ^b
CGI	2.00 ^c , 4 ^d	1.00 ^c , 1.00 ^d	1.00±.00	<0.000 ^a	<0.001 ^b	<0.001 ^b
BDNF-ng/ml	101.19 ^c , 45.12 ^d	103.26 ^c , 62,38 ^d	128.95±61.20	0.042 ^a	0.022 ^b	0.204 ^b
GDNF-pg/ml	0.46 ^c , 0.23 ^d	0.46 ^c , 0.23 ^d	.51±.61	0.900 ^a	0.003 ^b	0.001 ^b

HDRS: Hamilton depression rating scale, CGI: Clinical global impression scale, BDNF: Brain-derived neurotrophic factor, GDNF: Glial cell derived neurotrophic factor, P1: Comparison of before and after rTMS, P2: Comparison of control and patients before rTMS, P3: Comparison of control and patients after rTMS, ^a Wilcoxon signed rank test, ^bMann-Whitney U-test, ^cMedian values, ^dIQR values.

Table II: Comparison of patient and control stroop test scores before and after rTMS treatment.

	Before rTMS Mean±SD / Median, IQR	After rTMS Mean±SD	Control (n=33)	P1	P2	P3
Stroop 1/time	12.20±2.79	10.95±2.23	9.14±1.70	.001 ^a	.000 ^c	.000 ^c
Stroop 2/time	12.29±2.85	11.76±.3.66	9.74±.2.06	.197 ^a	.000 ^c	.007 ^c
Stroop 3/time	16.12±4.80	14.12±3.84	12.45±2.58	.002 ^a	.000 ^c	.042 ^c
Stroop 4/time	22.57±7.14	19.15±7.08	17.23±3.97	.001 ^a	.000 ^c	.179 ^c
Stroop 5/time	28.21 ^e , 12.31 ^f	27.79±8.39	25.32±6.41	.000 ^b	.001 ^d	.308 ^d

P1: Comparison of before and after rTMS, P2: Comparison of control and patients before rTMS, P3: Comparison of control and patients after rTMS, ^bWilcoxon signed rank test, ^cIndependent sample t test, ^aMann Whitney U-test, ^eMedian values, ^fIQR values.

In the current study, an improvement in cognitive functions and an increase in the levels of neurotrophic factors were found after rTMS treatment; however, there was no statistically significant correlation between the two events. Stimulation of the left DLPFC with rTMS was reported to result in cortical thickness of paralimbic cortex.²¹ Moreover, rTMS was thought to increase neurogenesis in the hippocampus and surrounding limbic structures and affect the level of neurotrophic factors, similar to antidepressants and ECT.

The present study has some limitations. All patients were treated with pharmacological agents before and during the rTMS treatment. As certain drugs can have positive or negative effects on cognitive functions and interact with rTMS, medications may have affected some of the results presented here. A sham control group was not used in the current study. Numerous studies have shown an increase in BDNF levels following lifestyle changes. The effects of lifestyle differences, such as walking or other forms of exercise on serum BDNF and GDNF levels, were not assessed in this study. The authors were unable to exclude the learning effect in neurocognitive tests that were applied to the patients after rTMS treatment; and did not use power analysis for determining the sample size.

Future studies are needed with the inclusion of a sham-control cohort and larger samples, which can exclude variables that may affect the levels of neurotrophic factors.

CONCLUSIONS

Combination of rTMS to antidepressant treatment led to an improvement in depressive and cognitive symptoms and an increase in serum BDNF and GDNF levels in treatment-resistant MDD patients. However, serum BDNF and GDNF levels did not show any statistically significant association with

depressive symptoms.

Adding rTMS to antidepressants is likely to be an appropriate treatment option for depressive patients with cognitive impairment as it contribute to the antidepressant effect by normalising serum BDNF and GDNF levels.

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ETHICAL APPROVAL:

The present study was approved by the Ethics Committee of the Faculty of Medicine, Karatay University, Konya, Turkey (No. 41901325-050.99).

PATIENTS' CONSENT:

Informed consents were obtained from all patients.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

DD, IEC, IE, : Designed the study and wrote the protocol.
 DD, IEC: Managed searches and analyses.
 DD: Responsible for recruitment of subjects.
 DD, IEC: Undertook statistical analysis.
 HK: Took part in the biochemical analysis.
 DD, IEC: Wrote the first draft of the manuscript.
 All authors contributed to, and approved the final manuscript.

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