

# Is transcranial magnetic stimulation effective in treatment-resistant combat related posttraumatic stress disorder?

Taner Oznur, MD, Süleyman Akarsu, MD, Cemil Celik, MD, Abdullah Bolu, MD, Barbaros Ozdemir, MD, Bülent D. Akcay, MD, Süleyman Ozselek, MD, Ali Bozkurt, MD, Kamil N. Ozmenler, MD.

## ABSTRACT

**الأهداف:** إظهار مدى فعالية التحفيز المغناطيسي المتكرر عبر الجمجمة في علاج حالات الاكتئاب الشديد المرافق لاضطراب الإجهاد ما بعد الصدمة المستعصية والمقاومة للعلاج.

**الطريقة:** تم جمع بيانات 20 من المرضى الذكور الذين كانوا يعانون من اضطراب الإجهاد ما بعد الصدمة المرتبط بالقتال، حيث تمت متابعتهم سريريا في قسم الإجهاد ما بعد الصدمة، القسم النفسي في أكاديمية جولهانه الطبية العسكرية خلال الفترة من يناير 2011م حتى ديسمبر 2012م بالإضافة إلى العلاج الدوائي تم إجراء التحفيز المغناطيسي المتكرر عبر الجمجمة. تم تحديد هذه البيانات عن طريق ملفات المرضى و سجلات المستشفى الحاسوبية.

**النتائج:** ظهر انخفاض واضح حسابياً في مقياس أثر الحدث في معدل فرط التيقظ. ومع ذلك لم تكن هناك فروق ذات دلالة إحصائية في مجموع مقياس أثر الحدث ومعدل التجنب ومعدل التدخل ومعدل بيك للاكتئاب ومعدل بيك للتوتر قبل وبعد التحفيز المغناطيسي المتكرر عبر الجمجمة.

**خاتمة:** تظهر فعالية التحفيز المغناطيسي المتكرر عبر الجمجمة في خفض أعراض فرط التيقظ إمكانية استخدامه في حالات الإجهاد ما بعد الصدمة المقاومة للعلاج. وينبغي تحديد دور التحفيز المغناطيسي المتكرر عبر الجمجمة في التدبير السريري للاضطرابات ما بعد الصدمة عبر دراسات شاملة أخرى.

**Objective:** To examine the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in patients with treatment-resistant posttraumatic stress disorder (PTSD) with co-occurring major depression.

**Methods:** We examined data on 20 male combat related PTSD patients admitted to the Post Traumatic Stress Disorder Clinic of Gülhane Military Medical Academy, Ankara, Turkey between January 2011 and December 2012 that received rTMS in addition to medical therapy. We obtained the data by examining the case files and hospital computer records.

**Results:** Decreases in the Impact of Event Scale (IES) hyperarousal scores were statistically significant. However, there were no statistically significant differences between the total IES scores, IES intrusion scores, IES avoidance scores, Beck Depression Inventory, and Beck Anxiety Inventory scores before and after rTMS treatment.

**Conclusions:** The efficacy of rTMS on the hyperarousal symptoms indicated that rTMS could be used in the treatment of patients with treatment-resistant PTSD. The role of rTMS in the clinical management of PTSD should be identified in further comprehensive studies.

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*From the Department of Psychiatry (Oznur, Celik, Ozdemir, Bozkurt, Ozmenler), Gülhane Military Medical Academy, Ankara, the Department of Psychiatry (Akarsu, Ozselek), Aksaz Military Hospital, Marmaris, the Department of Psychiatry (Bolu), Eskisehir Military Hospital, Eskisehir, and the Department of Psychiatry (Akcay), Konya Military Hospital, Konya, Turkey.*

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*Address correspondence and reprint request to: Dr. Taner Oznur, Department of Psychiatry, Gülhane Military Medical Academy, Etlik 06018, Ankara, Turkey. Tel. +90 (312) 3044501. Fax. +90 (312) 3044507. E-mail: drtaneroznur@gmail.com*

Repetitive transcranial magnetic stimulation (rTMS) is emerging as a potentially effective treatment for neuropsychiatric illnesses. An electrically generated magnetic field crosses the various tissues to reach the brain without causing convulsions or cognitive impairment, but causes depolarization of neurons.<sup>1</sup> The rTMS of the left dorsolateral prefrontal cortex (DLPFC) has been shown to be safe and efficacious in patients with

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depression, with overall response rates (>50% decrease in symptom severity) of 20-30%.<sup>2-6</sup> The application of low-frequency rTMS to the right DLPFC was found to be effective in lowering core PTSD symptoms and depressive symptoms.<sup>7</sup> However, the efficacy of rTMS in patients with treatment-resistant combat related PTSD has been not investigated. Therefore, in this study we examined the effect of rTMS in patients with co-occurring major depression and treatment-resistant combat related PTSD.

**Methods. Study subjects.** The data of 20 male patients admitted as an inpatient or outpatient to the Post Traumatic Stress Disorder Clinic of Gülhane Military Medical Academy, Ankara, Turkey between January 2011 and December 2012, and had received rTMS in addition to medical therapy were examined. We obtained the patient data by examining the patient files and hospital computer records. The data included; age, gender, elapsed time after trauma, rTMS protocol features, and side effects of the treatment. The data was then transferred to a computer database. Patients were eligible for the study if they met the following criteria according to the patient files: a) Diagnoses of combat related treatment-resistant PTSD and co-morbid major depression according to the Structured Clinical Interview, for DSM-IV Axis I Disorders, Clinician Version (SCID-I);<sup>8</sup> b) received rTMS treatment in addition to the current treatment; c) age 20 to 40 years; d) able to sign an informed consent. Patients were excluded from the study if they had met any of the following criteria: a) metal in the head or scalp; b) implantable devices including cardiac pacemakers and defibrillators; c) seizure within the past year; d) substance abuse within 3 months prior to rTMS; e) acute medical illness; f) epileptiform abnormalities on EEG. The review board at Gülhane Military Medical Academy, Ankara, Turkey approved this study. The management of the institution provided the required permission for the examination of patient files. The study was designed based on the Principles of the Helsinki declaration.

**Procedures.** Physical and biochemical examinations were carried out to exclude comorbid medical illness. An EEG was administered to rule out epileptiform abnormalities. If nonspecific abnormalities (such as diffuse slowing) were found, a CT scan or MRI scan of the brain was performed to exclude structural brain lesions. After a complete description of the rTMS treatment had been given to the subjects, written informed consent was obtained from all patients. The Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and the Impact of Event Scale (IES-R)

were administered to each of the patients before and after the rTMS treatment and they were kept in the patient files. The IES-R was applied to assess self-reported PTSD symptomatology experienced in the past 7 days.<sup>9</sup> The BDI was administered to measure depression severity.<sup>10</sup> The BAI is a self-report scale, and increasing scores indicates increasing intensity of anxiety symptoms.<sup>11</sup>

The rTMS protocol was applied in the form of the design that Boggio et al,<sup>12</sup> and Watts et al<sup>7</sup> used. The rTMS was provided using a Magstim Rapid stimulator (Magstim Company Ltd., Whitland, United Kingdom) with stand-held 70-mm figure-of-8 coils. On all occasions, the coil was held tangential to the scalp with the handle pointing back and away from the midline at 45° at the right DLPFC. The position of the right DLPFC was defined as 5 cm anterior (in a parasagittal line) to the motor cortex. The resting motor threshold was measured bilaterally with standard electromyogram methods.<sup>13</sup> The rTMS was administered at 80% of motor threshold, 40 stimulations per minute, for 15 minutes daily over 20 working days. Stimulation rates were 1Hz (40 s stimulation, 20 s rest per minute). Patients were maintained on unchanged antidepressant therapy during the rTMS treatments and for 2 months afterward. The patients continued to receive the same individual and group supportive psychotherapy.

**Statistical analysis.** Continuous variables were expressed as mean and standard deviation. The scores of pretreatment and posttreatment psychopathology, BDI, BAI, and IES were analyzed with Wilcoxon signed-ranks test. Statistical analyses were performed using the Statistical Package for Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA). A *p*-value <0.05 was considered for statistical significance, and 95% confidence intervals for mean.

**Results.** The subject group consisted of 20 males with a mean age of 28.7 (±3.3) years. The trauma types of all patients were combat reaction. The mean time elapsed since the trauma was 7.3 (±3.1) years. According to the hospital records, 4 patients among the participants reported the occurrence of mild headaches. No patients reported problems with memory or attention. The rTMS had no effect on any of the patient's blood pressure or heart rate during the treatments. The patients were distinctly treatment-refractory patients who had not responded to many years of psychopharmacology or various psychotherapies. All of the patients received one Hz rTMS to the right DLPFC. The mean BDI scores were 32.0±18.4 before rTMS treatment, and 27.0±10.4 after rTMS treatment (*p*=0.3). The mean

**Table 1** - Changes in scores before and after rTMS treatment among treatment-resistant PTSD patients.

Scores	Pretreatment	Posttreatment	Statistical analysis
BDI	32.0±18.4	27.0±10.4	Z=0.1; p=0.3
BAI	35.8±12.1	33.6±9.9	Z=0.1; p=0.3
IES total	62.0±10.9	57.0±11.1	Z=1.2; p=0.2
IES intrusion	21.4±5.4	21.2±3.7	Z=0.2; p=0.9
IES avoidance	19.2±2.4	16.8±3.9	Z=1.4; p=0.1
IES hyperarousal	21.4±4.7	19.0±4.2	Z=2.2; p=0.02

rTMS - repetitive transcranial magnetic stimulation,  
BDI - Beck Depression Inventory, BAI - Beck Anxiety Inventory,  
IES - Impact of Event Scale, PTSD - posttraumatic stress disorder,  
Z - Wilcoxon signed-ranks test

BAI pretreatment scores were 35.8±12.1, and post treatment mean scores were 33.6±9.9 ( $p=0.3$ ). Although there were decreases in IES scores, only decreases in the IES hyperarousal scores were statistically significant ( $p=0.02$ ) (Table 1).

**Discussion.** Posttraumatic stress disorder is often accompanied by comorbid psychiatric disorders.<sup>14,15</sup> Studies evaluating the onset of PTSD and major depression suggested that depression emerged often “secondary” to PTSD.<sup>16</sup> Depression was strongly associated with the severity of the combat.<sup>16</sup> Therefore, an effective treatment for PTSD may have an effect on the depression developed secondary to PTSD. Although antidepressant medications have often been used in the treatment of PTSD,<sup>17</sup> some patients do not respond and resistance to treatment may develop.

In this study, we aimed to determine the effectiveness of rTMS in patients with treatment-resistant PTSD co-occurring major depression. In an attempt to explain the results of the study, several variables such as frequency and location of stimulation of rTMS should be discussed. Several findings suggested that the right hemisphere, especially the right paralimbic and limbic structures are involved in the emotional and cognitive symptoms associated with traumatic memories.<sup>18,19</sup> Therefore, we stimulated the right DLPFC, similar to McCann et al.<sup>20</sup> The effects of rTMS on cortical excitability may depend on the frequency of stimulations.<sup>21</sup> The rTMS to the motor cortex has been reported to increase the excitability of some cortical neurons when delivered at high frequencies, or depress excitability at low frequencies.<sup>21</sup> The “Valence-hypothesis” has been formerly proposed for human anxiety.<sup>22</sup> According to this hypothesis, there is increased right-hemispheric

activity in anxiety disorders.<sup>22</sup> Low-frequency rTMS to the right DLPFC might have an anxiolytic effect and might normalize interhemispheric disbalance in anxiety disorders by reduction of right prefrontal activity.<sup>23,24</sup> If low-frequency rTMS could decrease activity in right hemispheric cortical areas, it might prove helpful in improving functional brain abnormalities associated with PTSD.<sup>25</sup>

McCann et al<sup>20</sup> showed that the application of low-frequency rTMS over the right DLPFC with a frequency of one Hz led to a marked improvement in PTSD core symptoms in contrast to 20 Hz rTMS. The rTMS delivered at one Hz to the right DLPFC resulted in statistically and clinically significant improvements in core PTSD symptoms and depressive symptoms compared with sham treatments.<sup>7</sup> In contrast to prior reports, 10 Hz rTMS to the right DLPFC improved both core symptoms of PTSD (re-experiencing and avoidance) and overall anxiety levels, whereas the low frequency group did not improve.<sup>26</sup>

According to the results of this study, decreases in the IES hyperarousal scores were statistically significant. This finding was compatible with the results of a previous study that indicated rTMS was effective especially on hyperarousal symptoms.<sup>25</sup> In the rTMS applications, statistically significant changes were not observed in the intrusion and avoidance subscale scores of IES. This finding was compatible with the findings of Cohen et al.<sup>26</sup> As discussed before, these results could be influenced by the implementation of rTMS.

The effectiveness of rTMS on the anxiety and depression scores in the patients was not determined in this study. The rTMS applications on veterans were effective for PTSD and depressive symptoms.<sup>7</sup> Additionally, potential therapeutic effects of rTMS for anxiety disorders have been reported.<sup>27</sup> The reason for the ineffectiveness of rTMS on general anxiety and depression levels may be the maintenance of avoidance and intrusion symptoms despite treatment.

The major limitation of this study is the retrospective design with no control group and no blinding, so the results must be considered exploratory. Another limitation of this study is the small number of subjects who participated. Additionally, the effects of gender on rTMS could not be assessed because all the patients were male.

In conclusion, the efficacy of rTMS on hyperarousal symptoms indicated that rTMS could be used in the treatment of patients with treatment-resistant PTSD. Although several studies investigating the effectiveness of rTMS in PTSD patients have been carried out, a rational and generally accepted rTMS protocol

has not been established. Discrepancies between the results of studies could be considered to be due to the clinical profiles of PTSD patients (comorbidity, treatment resistance, trauma type) and methodological differences (location, intensity, frequency, interval, and length of treatment). The role of rTMS in the clinical management of PTSD should be identified in further comprehensive studies designed to be sham-controlled, double-blind, and randomized.

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