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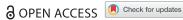
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ABSTRACT

Objective: The aim of this study was to evaluate the efficacy of repetitive transcranial magnetic stimulation (rTMS) in patients with treatment-resistant major depression and to explore the relationship between the outcome and comorbid anxiety symptoms.

Methods: The study was performed on 36 patients with treatment-resistant major depression. Patients received 15 rTMS sessions to their left dorsolateral prefrontal cortex with 110% motor threshold intensity, 20 Hz frequency, and 1000 pulses per day over a three-week period with the same stimulation parameters. Patients were assessed using Sociodemographics Form, the Montgomery–Asberg Depression Rating Scale (MADRS), and the Hamilton Anxiety Rating Scale (HAM-A) at baseline both before initiating rTMS treatment and on the first day following their last rTMS treatment session.

Results: Decreased scores in patients' MADRS and HAM-A (including subscales) were statistically significant with large effect sizes ($r > 0.5$) after rTMS treatment. Pretreatment HAM-A total scores and HAM-A somatic subscale scores were significantly higher in those who responded to rTMS ($p = .046$, $p = .048$). There were negative correlations between post-treatment MADRS scores and pretreatment HAM-A somatic and psychic subscale scores.

Conclusions: While the main limitations of the study are its design and small sample size, the findings suggested that comorbid anxiety symptoms, particularly somatic anxiety, could predict the response to rTMS in treatment-resistant major depressive disorder.

Introduction

Major depressive disorder is one of the main psychiatric disorders that threatens the health of the general public and is the second leading cause of disability in those aged 15–45 years, irrespective of gender [1,2]. Studies have estimated that by the year 2020, major depressive disorder will take second place overall among the causes of global disability in developed countries [3].

Somatic symptoms are common in those with affective disorders, including both major depressive disorder and anxiety disorders [4]. One international study showed that more than half of depressed patients have also reported somatic symptoms that were not explained by an organic etiology [5]. Depressive and somatic symptoms have been reported to be reciprocally predicted, while some patients may report predominantly somatic symptoms and deny any emotional distress or depression [4,5]. Anxiety disorders are the most concurrent psychiatric disorders in terms of the comorbidity of major depressive disorder, and the World Health Organization has emphasized that the comorbidity of anxiety disorders and depression is the most common psychiatric comorbidity [6]. In one study, it was reported that 40% of patients with major depression also had an anxiety disorder, while 45% of patients with a panic disorder had concurrent depression [7]. Furthermore, the comorbidity of anxiety and depression has been reported as a negative predictor of depression treatment response, leading to higher rates of treatment resistance and poor outcomes [8].

Many studies have shown that rTMS is a highly effective method in 20–40% of cases involving individuals that have been diagnosed with a medication-resistant major depressive disorder [9]. The modulation of neuronal activity by increasing or decreasing cortical excitability is the main effect of rTMS in an applied region. Moreover, neuroplasticity, modulation in the secretion of endogenous dopamine, and some neurotrophic factors, like brain-derived neurotrophic factor and an alteration of serotonergic and dopaminergic receptor levels, are likely the main components that are involved in the rTMS' mechanisms of action [10–13]. Although there are some reports determining the association between rTMS and brain regions (like the prefrontal cortex and amygdala) that are considered to be relevant to the pathophysiology of anxiety and

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depression, current studies investigating the therapeutic effects of rTMS in the treatment of anxiety disorders are unsatisfactory and contradictory [14]. Some studies have shown that rTMS is a promising tool for the treatment of anxiety spectrum disorders and anxious depression [15–18]. The purpose of this study, however, was to investigate the efficacy of high-frequency rTMS when applied to the left dorsolateral prefrontal cortexes (DLPFC) of patients in terms of alleviating their depressive symptoms and anxiety symptoms. This was achieved by carrying out pretreatment and post-treatment comparisons of 36 patients with medication-resistant major depressive disorder.

Methods

This study was conducted on 36 patients who had been diagnosed with treatment-resistant unipolar depression and who planned to undergo rTMS and were under observation by the GATA Haydarpasa Training Hospital, Department of Psychiatry as inpatients or outpatients. Patients who were aged between 18 and 52 years, right-handed, and literate were included in this study. All the patients met the criteria for non-psychotic unipolar depression as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [19] assessment. The patients were also required to have treatment-resistance, which was defined as not responding to adequate courses of at least one antidepressant, meet the criteria for a current major depressive episode, and have not had any changes in medication in the preceding eight weeks.

Subjects with psychiatric disorder due to a general medical condition, neurological disorders, a history of seizure or epilepsy, substance use disorders, bipolar or psychotic depression, psychotic spectrum disorders, or who had pacemakers, intracranial implants, and magnetic-sensitive objects were excluded from this study, as were privates in compulsory military service and military academy students. The study was performed in accordance with the Declaration of Helsinki and was approved by the Istanbul University Faculty of Medicine Local Ethics Review Committee (14.10.2011/03).

The use of rTMS therapy was explained to the patients and written informed consent was obtained from each participant before undergoing the rTMS course. A semi-structured interview, including the collection of sociodemographic data and clinical variables, was conducted with each participant individually. The Montgomery–Asberg Depression Rating Scale (MADRS) [20] and the Hamilton Anxiety Scale (HAM-A) [21] were used for clinical assessment, while the somatic (HAMA-S) and psychic (HAMA-P) subscales of HAM-A were evaluated separately in order to distinguish between the dimensions of the anxiety complaints. These two scales (MADRS and HAM-A) were performed before the start of the rTMS treatment protocol and one day after the last rTMS session. The patients' current medications were maintained throughout the study.

Using a Magstim Rapid[2] Brain Stimulator (Magstim Company Ltd, Whitland, London) with a double 70 mm air-cooled coil, rTMS was administered to the participants. The rTMS sessions were given on five consecutive days each week for three consecutive weeks. The sessions were performed by a highly trained psychiatrist in a private room designed for somatic therapies, located at the GATA Haydarpasa Training Hospital's Department of Psychiatry. The resting motor threshold was determined by the application of the motor evoked potential protocol 5 cm lateral to the interauricular line from the vertex, while observing the consecutive involuntary contractions of the contralateral abductor pollicis brevis muscle. All patients underwent 15 rTMS sessions and received a total of 15,000 pulses with a protocol consisting of a 20 Hz frequency, 1000 pulses per day (20 trains of 2.5 second duration and 50 pulses for each train), and 110% of the motor threshold intensity to the left DLPFC. The site of stimulation was defined as 5 cm anterior to the site of motor threshold in a parasagittal plane. This site was accepted as the left DLPFC. This method, also known as the "5 cm method," is the most commonly preferred and accepted method for the determination of the stimulation site in rTMS practice [22]. Upon defining the stimulation area, the coil was positioned 45 degrees away from the sagittal plane. Each session lasted about 15–20 minutes with the duration of sessions changing depending on the intensity of the treatment.

Side effects were checked and observed by a clinician in each session, and all of the subjective complaints reported by the patients and the side effects observed were recorded on a semi-structured interview form during the treatment course. *Treatment response* was defined as a 50% reduction in the patient's MADRS and HAM-A scores from the baseline, while the *remission criteria* included a score of 10 or less on the MADRS scale and 7 or less on the HAM-A scale.

The Statistical Package for the Social Sciences (SPSS) for Windows (version 16) was used to carry out all of the statistical analyzes. The statistical significance level was accepted as $p < .05$. The non-parametric Wilcoxon signed-rank test was conducted to evaluate the differences in baseline and post-treatment MADRS and HAM-A scores. A comparison of the HAM-A scores between MADRS <50% and ≥50% reduction groups was statistically analyzed using the non-parametric Mann–Whitney U test in order to determine the association between the antidepressant treatment outcome and anxiety symptoms. Effect size values below 0.3 were accepted as small effect, 0.3–0.5 as medium effect; values above 0.5 were accepted as

large effect. An overall 5% type I error level was used to infer statistical significance.

Results

In total, 36 patients completed the study: 55.6% were women and 44.4% were men. The mean age of the patients was 39.6 ± 9.1 years and the median duration of their last depressive episode was 2.25 (interquertile range [IQR] 1.5–6) months. The median number of lifetime depressive episodes was 3 (IQR 2–4) and the median disease duration was 4.5 (IQR 2–10) years. Two of the patients had histories of electroconvulsive therapy and they did not respond to rTMS treatment. Other sociodemographic characteristics are presented in Table 1.

The medications that the patients had taken before the last pharmacotherapy used during their enrollment in the study were assessed, and venlafaxine (75–300 mg/day) was found to be the most commonly used antidepressant agent, with a 28% ratio, while mirtazapine (15–30 mg/day) and sertraline (50–200 mg/day) were the second most commonly used, with 25% ratios. Venlafaxine was the most used antidepressant with a 36% ratio, while escitalopram was the second

most used antidepressant with a 19% ratio in the assessment of the patients' last medications. The shortest duration of treatment for the last medication was 40.3 ± 38.6 weeks, while the mean duration was 35.28 ± 7.29 weeks for the prior medications.

Treatment response was found in 15 patients (42%), thereby confirming that rTMS is an effective tool for treatment-resistant depression. Remission occurred in eight of the patients, at a rate of 22%.

The decreases in patients' MADRS and HAM-A scores (including subscales) were statistically significant with large effect sizes ($r > 0.5$) after rTMS treatment. The greatest change after rTMS treatment was observed in the MADRS score, with a 44% decline. The results are presented in Table 2.

While patients were divided into two groups: rTMS treatment responders (those who experienced a 50% reduction in their MADRS scores are accepted as responders) and non-responders, there was a significant difference between groups in terms of their pretreatment HAMA-S subscale and HAM-A total score (HAMA-T), but not of their HAMA-P subscale. The HAMA-S subscales and HAMA-T were statistically higher in the patients who responded to the rTMS treatment. These results are presented in Table 3.

A regression analysis was performed to determinate relationship between post-treatment MADRS score and HAM-A scores. The R^2 was calculated to be 0.865. There was a negative relationship between the post-treatment MADRS score and the pretreatment HAMA-S and HAMA-P subscales as a result of the regression analysis. The results are presented in Table 4.

The side effects that emerged during the study were expected, and the reported side effects were consistent with the rTMS side effect profile; however, epileptic seizure, the most severe of the reported side effects of rTMS, was not observed in any of the study subjects

Table 1. Sociodemographic characteristics and the clinical features of the patients.

		Frequency	%
Gender	Female	20	55.6
	Male	16	44.4
Marital status	Single	3	8.3
	Married	31	86.1
	Divorced/widow	2	5.6
Educational status	Unschooled	2	5.6
	Elementary school	7	19.4
	Secondary school	3	8.3
	High school	6	16.7
	University	18	50.0
Occupation	Unemployed	2	5.6
	Housewife	12	33.3
	Government employee	16	44.4
	Self-employed	4	11.1
	Retired	2	5.6
Monthly income	0–250 $	13	36.1
	250–500 $	1	2.8
	500–750 $	1	2.8
	750–1000 $	3	8.3
	1000–1250 $	8	22.2
	>1250 $	10	27.8
History of ECT	No	34	94.4
	Yes	2	5.6
History of rTMS	No	36	100.0
Suicide attempt	No	29	80.6
	Yes	7	19.4
Self-mutilation	No	35	97.2
	Yes	1	2.8
Familial history of depression	No	28	77.8
	Yes	8	22.2
Pain complaints	No	15	41.7
	Yes	21	58.3
Other psychosomatic complaints	No	14	38.9
	Yes	22	61.1
Substance use	No	36	100.0
	Total	36.00	100.0

Note: ECT: electroconvulsive therapy;
rTMS: repetitive transcranial magnetic stimulation.

Table 2. Baseline and post-treatment HAM-A and MADRS scores of the patients.

		Wilcoxon test statistics		Effect size
	Median (min, max)	z	p	r
HAMA-P (baseline)	12 (7, 17)	−4.92	<.001*	0.82
HAMA-P (post-treatment)	6 (2, 14)			
HAMA-S (baseline)	15 (5, 24)	−4.79	<.001*	0.79
HAMA-S (post-treatment)	8 (0, 16)			
HAMA-T (baseline)	27 (13, 40)	−5.02	<.001*	0.83
HAMA-T (post-treatment)	17 (2, 29)			
MADRS (baseline)	32 (20, 45)	−5.234	<.001*	0.87
MADRS (post-treatment)	18 (4, 38)			

Note: HAM-A: Hamilton anxiety scale, P: Psychic, S: Somatic, T: Total;
MADRS: Montgomery–Asberg depression rating scale.

Table 3. Comparison of HAM-A scores with respect to rTMS treatment response (≥ %50 reduction in MADRS scores).

	rTMS non-responders Median (min, max)	rTMS responders Median (min, max)	Mann–Whitney U		Effect size
			z	p	r
HAMA-P (baseline)	10 (7,16)	12 (8, 17)	−1.343	.179	
HAMA-S (baseline)	12 (5,24)	17 (6, 23)	−1.979	.048	0.32
HAMA-T (baseline)	25 (13,36)	29 (17, 40)	−1.998	.046	0.33
HAMA-P (post-treatment)	10 (5,14)	5 (2, 9)	−3.371	.001	0.56
HAMA-S (post-treatment)	10 (3,16)	8 (0, 12)	−2.388	.017	0.39
HAMA-T (post-treatment)	18 (9,29)	11 (2, 18)	−3.331	.001	0.55

Note: HAM-A: Hamilton Anxiety Scale, P: Psychic, S: Somatic, T: Total; rTMS: repetitive transcranial magnetic stimulation.

[23,24]. The most common side effects were as follows: headache in eight patients (22%), dizziness in four patients (11%), and lacrimation in three patients (8%). Only one patient dropped out of the study due to side effects or intolerance.

Discussion

As a result of this study, it has been determined that rTMS is an effective tool in the management of treatment-resistant unipolar depression, as well as in reducing the somatic symptoms of comorbid anxiety. The pretreatment total anxiety scores and somatic scores were higher in patients who responded to the rTMS treatment than they were in the non-responders.

The patients' baseline median MADRS score was consistent with moderate depression. Additionally, the baseline median HAMA-T was compatible with concurrent moderate anxiety. It has been reported that the presence of concurrent somatic complaints in depression is a predictor of a better outcome in rTMS treatment [25] and our results confirmed this

Table 4. Relationship between post-treatment MADRS scores and baseline HAM-A subscale scores.

		Coefficients		
Model[a]		B	Standard error	Sig.
MADRS (Post-treatment)	Constant	2.714	3.191	.402
	HAMA-P (post-treatment)	1.581	0.273	.000
	HAMA-S (baseline)	−0.501	0.153	.003
	HAMA-S (post-treatment)	0.706	0.190	.001
	MADRS (Baseline)	0.618	0.128	.000
	HAMA-P (baseline)	−1.318	0.357	.001

Note: HAM-A: Hamilton anxiety scale, P: Psychic, S: Somatic, T: Total; MADRS: Montgomery–Asberg depression rating scale.
[a]A multiple linear regression model.

data. However, controversial data also exists as one review reported that the absence of anxiety symptoms in depression was a positive predictor of rTMS treatment response [26]. Not only are our results consistent with the data supporting the suggestion that rTMS may also be effective in treating anxiety symptoms in depression or comorbid anxiety disorders [15,16], but we also examined the patients' anxiety symptoms by using the HAM-A, which is a more extensive tool for assessing anxiety symptoms than the Hamilton Depression Scale which is a commonly used tool in the evaluation of anxious depression.

Therefore, in the current study, concurrent anxiety symptoms in depressed patients were examined more extensively than they have been in previous studies. Our results revealed that the participants' depressive and anxious symptoms including somatization decreased significantly after rTMS treatment, while their baseline somatic and psychic symptoms had a negative relationship with rTMS treatment response. We found no statistically significant differences in baseline psychic symptoms severity of anxiety when we compared rTMS treatment responders and non-responders. However, baseline somatic symptoms severity of anxiety in those who responded to rTMS treatment was significantly higher than non-responders. These findings support the hypothesis that in addition to somatic symptoms improve concurrently with depressive symptoms as a result of treatment, the somatic symptoms of anxiety are more prominent in terms of predicting treatment outcomes in depression. With regard to the recent data suggesting rTMS as a novel and promising tool in the treatment of anxiety disorders (as well as some physical illnesses, notably pain disorders), this stimulation method could be a useful option in the treatment of concurrent somatic symptoms and depression [27,28].

This study also confirmed that rTMS is a safe stimulation method in terms of the side effect profile; however, transient headache was found to be the most common side effect, which is consistent with the current data [2,29].

The limitations of this study include its open-label design without a sham-control group which precludes the ability to make definitive comments on causality, the study's small sample size, relatively short treatment duration, and low number of pulses. Moreover, another limitation is present with regard to our diagnosis of comorbid clinical anxiety disorder in the patients since we only evaluated their symptoms of anxiety.

We conclude that future double-blind sham-controlled studies with larger sample sizes that evaluate comorbid conditions, particularly anxiety symptoms, and subtypes of depression in those who respond to rTMS treatment are warranted in order to understand the underlying mechanisms of rTMS and make this promising, effective, and approved stimulation method

more beneficial in clinical practice with regard to identifying the patient groups that will likely benefit from such treatment.

Disclosure statement

No potential conflict of interest was reported by the authors.

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