The Impact of Repetitive Transcranial Magnetic Stimulation on Oxidative Stress in Subjects With Medication-Resistant Depression

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Objectives: Recent studies have shown that oxidative stress is involved in the neurobiology of depression. We investigated the effects of repetitive transcranial magnetic stimulation (rTMS) on a novel oxidative stress marker, thiol-disulfide homeostasis, in subjects with medication-resistant major depression (MRD).

Methods: Twenty-six subjects with MRD underwent 15 rTMS sessions. Sociodemographic and baseline and post-rTMS Montgomery-Asberg Depression Rating Scale (MADRS) data were collected. Serum levels of native thiol, total thiol, and disulfide and their pairwise ratios were measured in baseline and post-rTMS blood samples.

Results: Serum levels of native and total thiol were significantly decreased after rTMS treatment ($P < 0.05$). Serum levels of thiol-disulfide and their ratios did not significantly differ ($P > 0.05$) between rTMS treatment responders (>50% reduction in MADRS score, n = 11) and rTMS treatment nonresponders (n = 15). The percentage MADRS score changes did not correlate with the changes in the levels of serum thiol-disulfide from baseline to post-rTMS treatment in any subject ($P > 0.05$).

Conclusions: Our results showed that rTMS treatment was effective in subjects with MRD and was associated with changes in serum thiol levels regardless of improvement in depression severity. Thus, the results did not support a possible therapeutic relationship between rTMS and thiol-disulfide homeostasis in subjects with MRD.

Key Words: depression, oxidative stress, rTMS, thiol, disulfide

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Major depression, which is a mental health condition with a significant global burden, is projected to be the second most disabling disorder in the world by 2020.[1] In the last 2 decades, several studies have implicated different neurobiological mechanisms beyond the classic monoamine hypothesis in depression.[2] However, no conclusive models explain the underlying mechanisms of depression. Considering the complexity and heterogeneity of clinical depression, several neurochemical processes, including oxidative stress homeostasis, have been examined in recent research focused on establishing a depression model.[3] Oxidative stress is a condition that involves an imbalance between oxidant and antioxidant processes and that results in increased oxidative products, such as free radicals and reactive oxygen species, that cause severe cell damage.[4] Low antioxidant status or high oxidant stress has been linked to several systemic diseases, such as diabetes, cardiovascular events, atherosclerosis, and neurological diseases.[5,6] Several methods and parameters are used to determine oxidative stress status in humans.[7] Oxidative biomarkers are molecules that are modified by interactions with reactive oxygen species and in response to increased redox stress. Malondialdehyde and isoprostanes are the most studied markers of lipid peroxidation.[8] Oxidative protein modifications, which are quantified by measuring nitrotyrosine or S-glutathionylation, are potential oxidative markers. Myeloperoxidase, which is an enzyme involved in the formation of reactive oxygen species, is a well-established and promising oxidative stress marker.[9] Besides oxidative stress parameters that reflect the burden of oxidation, the net antioxidant capacity of serum can be measured by quantifying the activity of antioxidant enzymes, such as catalase, glutathione peroxidase 1, and superoxide dismutase, which are considered the most prominent markers of antioxidant capacity.[9] Total antioxidant status and the oxidative stress index are used to determine the circulating antioxidant capacity in serum samples. Although these assays are advantageous in terms of time efficiency, cost-effectiveness, and assessment comprehensiveness, they are restricted in determining specific enzymatic reactions.[10] Oxidative stress has been a focus of research in neuropsychiatric conditions, including cognitive impairments and depression. An investigation of the relationship between depression and oxidative stress has reported decreased total antioxidant capacity and increased peroxidation in blood samples of subjects with depression,[11] whereas other studies have reported contradictory findings.[12] Imaging and postmortem studies of depressed subjects have shown significant reductions in the regional volume of corticolimbic circuits owing to increased neural cell damage and decreased neuroplasticity.[13] Considering that conditions involving oxidative stress can damage cells, including neurons, recent studies have suggested that pathophysiological processes involving oxidant-induced neural damage might contribute to depression onset, but the findings remain inconsistent because of differences in the study designs.[3,4,13,14]

Increasing evidence of the neurobiology of depression has yielded novel modalities of antidepressant treatment. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive therapeutic tool that has been approved for use in medication-resistant depression.[15] The principle of rTMS is based on Faraday law, which states that an alternating magnetic field will produce electrical activity in an adjacent region.[16] With rTMS, the cerebral cortex is stimulated by vertically alternating magnetic pulses that are generated by an electric current that passes through a wire coil. The magnetic field induces electric activity in the cortex and changes the excitability of the stimulated area and its related circuits. The effects of rTMS on cortical excitability vary according to the parameters applied during the stimulation. The stimulation area, frequency, number of pulses, intensity, and intertrain interval are the main parameters used in this therapeutic application. Low-frequency protocols yield long-term depression in synaptic areas,

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which results in neuronal inhibition, whereas high-frequency protocols are associated with long-term potentiation and increased cortical excitability.[16] However, the underlying mechanisms of the therapeutic effects of rTMS are not fully understood. The following effects of rTMS have been reported: increased endogenous dopamine in the central nervous system; altered synaptic neuroplasticity and neurotransmitter receptor expression; increased expression of neurotrophic factors, such as brain-derived neurotrophic factor, and neurotransmitter receptor genes; alterations in blood flow and metabolism in the brain; and enhanced neuroprotection through dendritic spine remodeling and antiapoptotic effects.[16] Clinical and experimental associations have been reported between transcranial magnetic stimulation and reduced oxidative stress in neurological conditions, and this may possibly indicate a neuroprotective effect.[17,18] In addition to increasing evidence that oxidative stress markers, including antioxidants and oxidative damage products in blood samples, are dysregulated in depression, antidepressant treatment response is also associated with the normalization of the levels of these markers.[19] Furthermore, stimulation applications, such as electroconvulsive therapy, also change oxidative and inflammatory markers in neuropsychiatric conditions, including depression.[20,21]

Thiols, which are organosulfur compounds with active sulfhydryl bonds that are mainly formed by proteins and particular antioxidant barriers, act as reducing agents in humans.[22] Free oxygen radicals interact with thiols and are reduced by the formation of disulfide bonds, which are the products of the oxidized sulfhydryl compounds of the thiols.[22] In oxidization, the formation of disulfide bonds is increased whereas thiol levels are decreased. Disulfide bonds can return to thiol groups, and this interaction yields a dynamic thiol and disulfide formation in response to oxidative stress. In addition to managing antioxidant defense mechanisms, thiols play a critical role in detoxification, apoptosis, transcriptional mechanisms, and the regulation of enzymatic activation at the cellular level.[23] Dynamic thiol-disulfide homeostasis is a novel oxidative stress marker that is useful for determining thiol-disulfide exchanges.[23] This practical method involves the calorimetric measurement of plasma thiol and disulfide levels using a very accurate, very sensitive, and automated spectrophotometer. The dynamic thiol-disulfide homeostasis method reflects both oxidative stress and antioxidant capacity.[23] To the best of our knowledge, no studies have investigated the levels of oxidative stress markers, including thiol-disulfide exchanges, following a course of rTMS in subjects with depression. Therefore, we hypothesized that the suggested antioxidative effects of rTMS would be related to its therapeutic effects in subjects with depression. In this study, we examined the effects of rTMS on oxidative stress and antioxidant capacity in subjects with treatment-resistant depression to better understand the therapeutic mechanisms underlying rTMS.

MATERIALS AND METHODS

Before the study, a power calculation was performed based on the assumption that serum disulfide levels reflect disulfide bonds that are formed by thiol oxidation during increased oxidative stress. We calculated that a minimum of 30 subjects is required to detect an effect size of 0.50 in the comparison of serum disulfide levels at baseline and after rTMS application for a significance level of 0.05 and power of 0.80. The dropout rate was determined to be 10%.

Thirty subjects with diagnoses of unipolar major depression that were confirmed by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Axis I Disorders[24] were enrolled in the study. Four subjects dropped out owing to headaches and discomfort in the rTMS application area (n = 26). All participants were aged between 18 and 65 years, right-handed, and literate. Treatment resistance, which was defined as the lack of a response to at least 1 antidepressant treatment regimen with an adequate course and medication dosage, was required in all participants. The exclusion criteria for this study were depression with psychotic features, organic neuropsychiatric disorder, or bipolar disorder; substance use; any past or ongoing systemic disease, such as hypertension, atherosclerosis, ischemic cardiac disease, diabetes mellitus, or autoimmune/rheumatological/inflammatory disease; and conditions that contraindicated rTMS, such as history of epileptic seizures, increased intracranial pressure, a cardiac or intracranial implant, or having a ferromagnetic devices. The participants' most recent medications were maintained across the study, and the participants could not have changed their medication in the preceding 8 weeks. All participants provided written informed consent, and their anonymity was preserved after a detailed explanation of the study and rTMS procedures by a physician. The participants were also requested to inform the researcher if they acquired any additional medications during the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics review committee.

The rTMS protocol was defined as 15 sessions (5 consecutive days each week for 3 weeks) of rTMS application (frequency of 20 Hz, 110% of the motor threshold, and 1000 pulses per session [20 trains with 2.5-second durations and 50 pulses in each train]) to the left dorsolateral prefrontal cortex, the location of which was determined by the 5-cm method (5 cm anterior to the site of the motor threshold in the parasagittal plane). The motor threshold was determined by a visualization method in which the minimum intensity was defined after the standard motor-evoked potential protocol was applied 5 cm lateral of the vertex in the interauricular line to result in contralateral consecutive involuntary contractions in the contralateral abductor pollicis brevis muscle.[25]

At baseline and 1 day after the last rTMS session, a sociodemographic questionnaire that included clinical data from the Montgomery-Asberg Depression Rating Scale (MADRS)[26] was administered and blood samples were obtained. The blood samples were centrifuged at 1500 × *g* for 10 minutes, and serum samples were stored at −80°C until the assay. Dynamic disulfide bonds (−S-S) were reduced to free functional thiols (−SH) using sodium borohydride ($NaBH_4$). The remaining $NaBH_4$ reductant was removed and consumed by formaldehyde to accurately measure the total thiol amount. Mercaptoethanol solutions were used for calibration. Native thiol and total thiol levels were measured synchronously in a paired test. The disulfide bonds were quantified with a formula that included half of the value of the difference between the total thiol and native thiol amounts.[23] After determining the native thiol, total thiol, and disulfide amounts, the disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios were calculated from samples obtained at baseline and after the rTMS course. The treatment response criterion was defined as a 50% reduction in the MADRS score.

The data were evaluated using the Statistical Package for the Social Sciences (version 20.0; IBM Corporation, Armonk, NY). Because of the small sample size, the normality of the distributions was determined using Shapiro-Wilk tests. The descriptive data are presented as mean ± SD. χ^2 tests were used to compare the independent nominal variables, including sex, marital status, the presence of depression in first-degree relatives, and suicide attempts among the rTMS treatment responder and nonresponder groups. For cases with nonnormally distributed data, nonparametric Mann-Whitney *U* tests were used to compare the independent

continuous variables, including the age, the duration of depression, the baseline and post-rTMS MADRS scores, the levels of serum native thiol, total thiol, and disulfide, as well as their pairwise ratios, between the rTMS treatment responder and nonresponder groups. For the nonnormally distributed dependent continuous variables, nonparametric Wilcoxon signed rank tests were used to compare the baseline and post-rTMS MADRS scores as well as the levels of serum native thiol, total thiol, and disulfide and their pairwise ratios. In the correlation analyses, we examined the correlations between 2 continuous variables, and Pearson correlation tests were used to assess the linear relationships between the baseline MADRS scores and the baseline serum thiol-disulfide levels and between their change ratios after the rTMS. Differences were considered significant when the *P* values were less than 0.05.

RESULTS

Thirteen female (50%) and 13 male (50%) participants were involved in the study. The mean age of the participants was 39.9 ± 10 years. The mean duration of the participants' last depressive episode was 5 ± 7 months. Their mean number of lifetime depressive episodes was 3.1 ± 2.1, and the mean duration of their disease was 8.2 ± 8.5 years. During enrollment in the study, 5 of the participants were not being treated with concurrent medication, whereas 6 participants were regularly taking 1 psychotropic medication. The rest of the participants were taking 2 or more psychotropic medications. Half of the participants (n = 13) were hospitalized at least once, and 2 participants reported that they had undergone electroconvulsive therapy. None of the participants reported undergoing rTMS treatment before the study. The sociodemographic data, clinical features, and mean MADRS scores for the participants are shown in Table 1. The MADRS scores were significantly decreased after rTMS treatment in all participants.

TABLE 1. Sociodemographic Data, Clinical Features, and the Participants' MADRS Scores

Total No. Patients (N) = 26	n	%
Sex		
Female	13	50
Male	13	50
Marital status		
Single	3	11
Married	23	88
Presence of depression in 1st degree relatives		
Yes	5	19.2
No	21	80
History of hospitalization		
Yes	13	50
No	13	50
Suicide attempt		
Yes	3	11.5
No	23	88.5
	Mean	**SD**
Age	39.9	10
Duration of depression, y	8.2	8.5
No. lifetime depressive episodes	3.1	2.1
Duration of the last depressive episode, mo	5	7
Baseline MADRS score	32.8	5.8
Post-rTMS MADRS score	20.5	8.7

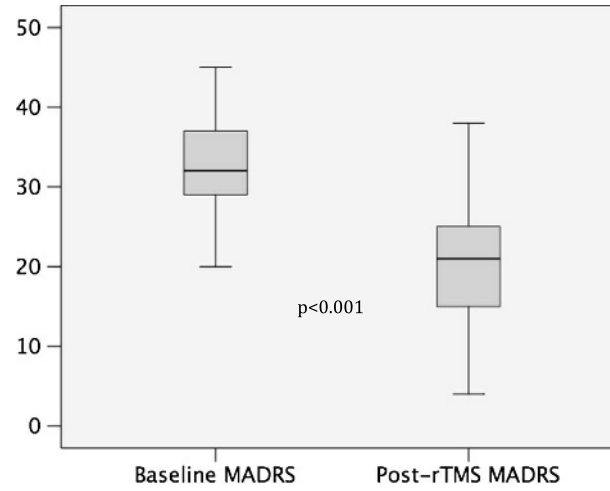

FIGURE 1. Comparison of the baseline and post-rTMS median MADRS scores of the participants.

The baseline MADRS score was 32.8 ± 5.8, and the post-rTMS MADRS score was 20.5 ± 8.7 ($z = -4.46$, $P < 0.001$, Fig. 1). Treatment response (>50% reduction in MADRS score) was determined in 42% of the participants (n = 11). No significant differences were found between rTMS treatment responders (n = 11) and nonresponders (n = 15) in terms of clinical features including sex, marital status, presence of depression in first-degree relatives, and suicide attempt as well as in the levels of serum native thiol ($P = 0.55$ for baseline and post-rTMS), total thiol ($P = 0.58$ for baseline; $P = 0.48$ for post-rTMS), and disulfide ($P = 0.75$ for baseline; $P = 0.46$ for post-rTMS) and the disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios ($P = 0.18$ for baseline; $P = 0.77$ for post-rTMS for all three ratios). Comparisons of the baseline and post-rTMS levels of serum native thiol, total thiol, disulfide levels, and their pairwise ratios (disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol) revealed significant decreases in serum native and total thiol levels after rTMS treatment ($z = -2.47$, $P = 0.01$ for native thiol; $z = -2.52$, $P = 0.01$ for total thiol; Fig. 2), whereas serum disulfide levels were nonsignificantly decreased ($P = 0.20$; Fig. 2). The thiol-disulfide pairwise ratios differed nonsignificantly between baseline and after rTMS treatment ($P = 0.99$ for disulfide/native thiol; $P = 0.90$ for disulfide/total thiol; $P = 0.90$ for native thiol/total thiol). No correlations were found between baseline serum thiol-disulfide measures and MADRS scores (Pearson correlation, $P > 0.05$, Table 2) and the percentage change in MADRS scores and serum thiol-disulfide measures from baseline to after rTMS treatment in all participants (Pearson correlation, $P > 0.05$, Table 2).

DISCUSSION

The results of our study showed that rTMS application in subjects with medication-resistant depression was effective for alleviating depressive symptomatology. Contrary to our expectations, we did not find any significant relationships between rTMS treatment response and serum thiol-disulfide levels and their pairwise ratios. However, the most notable finding regarding thiol-disulfide homeostasis was the significant decrease in serum native and total thiol levels after rTMS treatment, irrespective of treatment response. Thiol-disulfide homeostasis, which is a novel oxidative stress marker, has been reported to be impaired in the pathogenesis of various acute and chronic

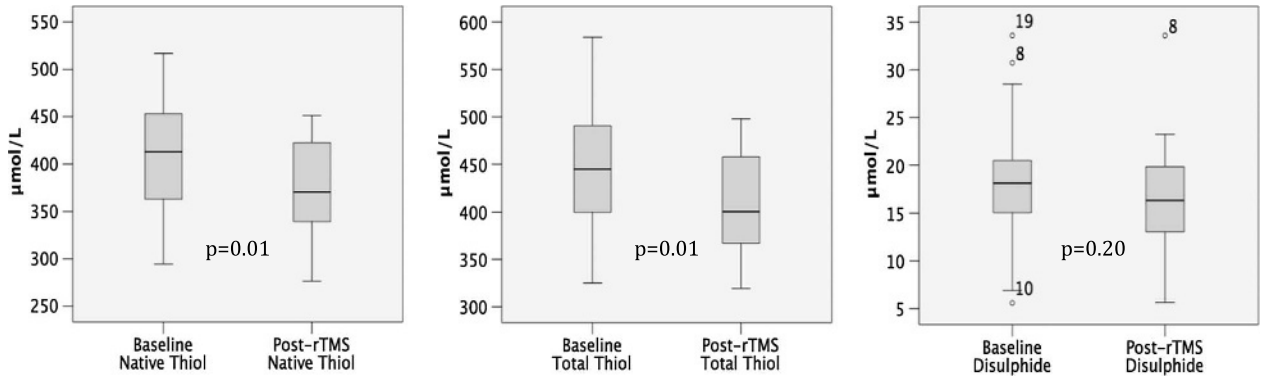

FIGURE 2. Distribution of the baseline and post-rTMS serum thiol-disulfide levels of the participants.

diseases.[23] Currently, no studies have examined thiol-disulfide imbalance in psychiatric conditions, including depression. The findings of several studies have suggested that oxidative stress measures other than thiol-disulfide homeostasis play a role in the neurobiology of depression and that antidepressant treatments improve oxidative stress and antioxidant capacity.[27,28] Inflammatory processes and oxidative stress are associated with a shift towards disulfide formation, whereas increased native and total thiol levels, which are major contributors to antioxidants, have been implicated in increased antioxidant capacity.[29] Previous studies have suggested that decreased thiol levels with concurrent increased disulfide levels reflect oxidative stress. One of the main findings in this study was a decrease in native and total thiol levels after rTMS treatment, which implied an oxidative stress status. However, we found that serum disulfide levels and disulfide/thiol ratios were also decreased concurrently, which was not in line with increased oxidative stress. Thus, we assumed that our findings were not consistent with oxidative stress status. This finding implied that rTMS treatment could be associated with decreased oxidant and antioxidant parameters independent of improvements in depression. Many studies that have been conducted on the neurobiology of depression have reported a relationship between oxidative stress and depression, but the data are not sufficient to reveal a causal relationship.[30] Whether changes in thiol-disulfide status are etiologic or a result of disease, we assumed that decreased thiol and disulfide levels were an outcome of decreased inflammatory processes or oxidative stress and, therefore, decreased antioxidant activity. However, oxidative stress has been related to reductions in synaptic plasticity and regional brain volumes in the hippocampus, amygdala, and prefrontal cortex that are involved in cognitive functions and depression pathogenesis.[31,32] As is well known, cognitive impairments are one of the most prominent clinical features observed in major depression. Furthermore, rTMS treatment is related to improvements in synaptic plasticity and cognitive impairments by modulating cortical excitability in several neuropsychiatric disorders, including depression.[16,33] These findings suggest that depression and cognitive deterioration develop because of oxidative stress in the central nervous system and that oxidative stress may be the shared mechanism in depression and cognitive deterioration. These results further prompted us to investigate the impact of rTMS application on oxidative stress and antioxidant capacity. However, our results were not adequate to conclude if rTMS treatment was associated with thiol-disulfide homeostasis in terms of the mechanisms of action in participants diagnosed with medication-resistant depression. In addition, we did not find any correlations between depression severity and thiol-disulfide measures at baseline or post-rTMS treatment. Taking into consideration the major limitations of this study, such as small sample size and lack of a control group, we assumed that this data also suggest that rTMS efficacy on depression severity may not be associated with the status of thiol-disulfide homeostasis.

Some limitations in this study need to be considered while interpreting the results. In addition to the considerably small sample size and lack of a control group, we measured oxidative and antioxidative parameters in peripheral blood samples that might yield limited data on oxidative status and the impact of rTMS on the central nervous system. Although the current medications of the participants were maintained during the study, we cannot exclude the influence of the ongoing medications on the levels

TABLE 2. Correlations Between the Baseline MADRS Scores and the Baseline Serum Thiol-Disulfide Levels and Between Their Change Ratios After rTMS

	Baseline Values											
	Native Thiol, µmol/L		Total Thiol, µmol/L		Disulfide, µmol/L		Disulfide/Native Thiol (%)		Disulfide/Total Thiol (%)		Native Thiol/Total Thiol (%)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
MADRS scores	−0.06	0.76	−0.08	0.68	−0.12	0.53	−0.03	0.87	−0.04	0.83	0.04	0.83
	Change Ratios (After rTMS)											
	Native Thiol, µmol/L		**Total Thiol, µmol/L**		**Disulfide, µmol/L**		**Disulfide/Native Thiol (%)**		**Disulfide/Total Thiol (%)**		**Native Thiol/Total Thiol (%)**	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
MADRS scores	−0.14	0.48	−0.16	0.41	−0.16	0.41	−0.11	0.56	−0.12	0.53	0.06	0.73

of the parameters measured in this study. Furthermore, given the lack of a sham condition, the possibility of a placebo effect on the influence of rTMS application on the serum levels of native and total thiol should also be taken into consideration when interpreting the results.

In conclusion, to the best of our knowledge, this is the first study to investigate the effects of rTMS treatment on thiol-disulfide homeostasis, a novel oxidative stress marker, in subjects with medication-resistant depression. Our results showed that rTMS treatment was an effective therapeutic tool in subjects with medication-resistant depression and was associated with changes in serum thiol levels regardless of improvement in the depression severity. We did not find any evidence for a therapeutic relationship between rTMS and thiol-disulfide homeostasis in subjects with medication-resistant depression. Additional studies with larger sample sizes are warranted to identify the effects of rTMS on oxidative/antioxidative status as well as the rTMS mechanisms of action to better understand the underlying pathophysiological pathways of depression and establish future therapeutic interventions.

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