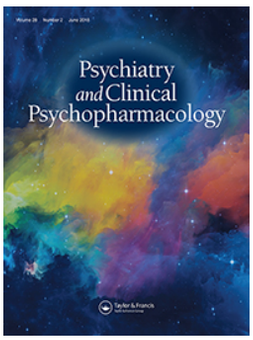

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The impact of high-frequency repetitive transcranial magnetic stimulation on executive functioning of drug-free patients with treatment-resistant depression

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ABSTRACT

OBJECTIVES: The aim of the present study was to examine the impact of 25 Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) on neuropsychological testing in treatment-resistant depression patients who were receiving no other concomitant medications for the treatment.

METHODS: A total of 19 patients with treatment-resistant depression and 20 healthy controls were included in the study. A 25 Hz, 1000 pulse stimulation was set at 100% of the motor threshold and delivered 20 times for 2 s with 30 s intervals as 20 sessions to the depression group, and sham treatment was applied to the control group. Brief Psychiatric Rating Scale (BPRS), Stroop task, trail-making test (TMT), and Wisconsin card sorting test (WCST) were performed both before and 3 days after the rTMS treatment. Seventeen-item Hamilton Depression Rating Scale (HAMD) and Beck Depression Inventory (BDI) were obtained at baseline and after the rTMS treatment, as well.

RESULTS: After the rTMS treatment, 52.6% (10 of 19 patients) met the response criteria (>50% improvement in HAMD score), with 5 (26.3%) patients meeting the criteria for remission of depression (HAMD score ≤ 8). None of the patients had a worsened HAMD score at the end of treatment. Reflecting the antidepressant effect of rTMS treatment, the mean BDI score, BPRS score, and Stroop task scores significantly differed following the treatment ($p < .001$, $p < .001$, and $p = .017$, respectively). TMT score difference did not reach statistical significance, whereas WCST scores showed significance in "correct responses" and "perseverative errors" categories ($p < .05$, and $p < .05$, respectively). None of the test scores at the end of rTMS treatment showed a significant difference when compared to baseline scores for the control group ($p > .05$, for all).

CONCLUSIONS: Results suggest that rTMS can be used as a beneficial treatment option to ameliorate cognitive functions, especially executive functions. Patients had an improvement in depressive symptoms with the rTMS treatment without any concomitant medication, as well. Therefore, improvement in cognitive performance might be associated with improvement in depressive symptoms.

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RTMS; treatment-resistant depression; Stroop test; Wisconsin card sorting test; trail-making test

Introduction

Repetitive transcranial magnetic stimulation (rTMS) therapy is a non-invasive brain stimulation technique that has proved to be associated with significant improvements in clinical symptoms of major depressive disorder either as monotherapy or combination therapy [1]. The repeated short bursts of magnetic energy introduced through the scalp excite neurons locally and connected areas in the brain [2]. This raises the interest of both patients and clinicians turning the current of clinical decision towards extensive consideration of rTMS as a treatment option in major depressive disorder treatment. The Food and Drug Administration (FDA) approved rTMS in subjects with major depression who had no sufficient response to a prior appropriate antidepressant medication in 2008 [3]. FDA clearance was based on a large, multisite, sham-controlled randomized study that showed that daily prefrontal TMS was a well-tolerated and effective treatment for certain patients with major depression.

The dorsolateral prefrontal cortex (DLPFC) is associated with executive functions, including working memory and selective attention and is a key node in attention networks [4,5]. Also, DLPFC is the most accessible area for stimulation that is related to brain regions known to be related to the pathophysiology of depression [6].

While rTMS has its own limitations, it can be quite effective for patients who do not tolerate medication treatment and are not willing to consider electroconvulsive therapy (ECT). A meta-analysis of 34 studies

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comparing rTMS to sham treatment for the acute treatment of depression showed an effect size of 0.55 ($p < .001$) [7]. This is comparable to commonly reported effect sizes of pharmacotherapeutic strategies for treatment of depression in the range of 0.17–0.46 [7]. George et al. [8] demonstrated that rTMS, as drug-free monotherapy, produced statistically significant antidepressant effects with a remission rate 4 times that of sham patients, in a multisite, randomized controlled trial [8].

High-frequency rTMS has promising effects in enhancing cognitive functions in neuropsychiatric disorders [9]. Ahmed et al. [10] confirmed that five daily sessions of high-frequency rTMS over the left and then the right DLPFC improves cognitive function in patients with mild to moderate degree of Alzheimer's dementia and this improvement was maintained for 3 months [10]. Kim et al. [11] recently published a paper demonstrating that daily 10-Hz frequency rTMS can improve attentional control in normally ageing individuals [11]. Significant improvement on a trail-making test (TMT) was shown by Moser et al. [12], in a sham-controlled study in elderly patients with refractory depression [12]. rTMS found to improve the perseverative errors on Wisconsin card sorting test (WCST) in patients with Parkinson's disease and concurrent depression [13].

The aim of the present study was to examine the impact of 25-Hz high-frequency rTMS on neuropsychological tests in treatment-resistant depression patients who were receiving no other concomitant medications for the treatment. It was hypothesized that "rTMS only" treatment would not lead to any deterioration in executive functions and even can reduce depression symptom severity and improve cognitive functions assessed by a standard cognitive test, when compared to baseline.

Materials and methods

Participants

A total of 20 patients with depression and 20 healthy controls underwent rTMS treatment from May 2013 to June 2013. One of these 20 patients never came to the hospital after the registration and withdrew from the study. No patients discontinued due to adverse events associated with the intervention. Finally, 19 patients completed the rTMS protocol. Participants were excluded for any of the following reasons: serious suicide risk; current substance use disorders (including alcohol abuse); psychotic disorders; seizure disorder; a history of head trauma; other neurological disorders; pregnancy; or any acute, unstable medical conditions that required stabilization; left-handedness; or having metal implants.

Procedure

This prospective study was approved by the local Institutional Review Board and the study protocol conformed to the Helsinki declaration. Outpatients from the Uskudar University Feneryolu Clinics who met the Structured Clinical Interview for DSM-IV criteria for major depression were included in the study, between May 2013 and June 2013. Written informed consent was obtained from all participants prior to enrolment. Patients included in the study were free of other medications for the treatment of depression since 2 months. As we studied with a treatment-resistant depression group, the patients were not administered any antidepressant during the study. "Treatment-resistant" criteria were described as a poor response to two adequate (optimal dosage and 6–12 weeks duration) trials of two different classes of antidepressants. Subjects had a complete neurological and physical examination. Participants in the control group were free of any neuropsychiatric medication, as well.

Stimulation

The rTMS consisted of a high-frequency (25 Hz) stimulation of the left prefrontal cortex deemed to be located 5 cm forward from the cortical motor area of the abductor pollicis brevis of which the motor threshold was determined. The rTMS was applied through a figure-8 coil connected to a magnetic stimulator, which provides a biphasic pulse (Magstim Company, Whitland, UK). The rTMS intensity was set at 100% of the motor threshold, which was determined by visual inspection. rTMS was applied daily for 20 consecutive days, except for Sundays. The stimulation consisted of 20 pulse trains of 2 s at 25 Hz, and separated by 30 s inter-train intervals. A session comprised 1000 magnetic pulses and a full course of treatment comprised 20 sessions. The control group subjects were stimulated with sham coil using the same procedure as the patient group.

Clinical and neuropsychological evaluation

Before and 3 days after the 20th session of rTMS, clinical response was assessed using the 17-item Hamilton Depression Rating Scale (HAMD) and Beck Depression Inventory (BDI). Neuropsychological tests were administered to assess executive function at baseline and 3 days after the 20th session of rTMS treatment. As the prefrontal cortex was the target stimulation area, three different tasks assessing frontal executive functions were used: Stroop task, TMT, and WCST.

Hamilton Depression Rating Scale

Depressive symptom changes were measured by validated HAMD [14]. The primary outcome parameter, the 17-item HAMD score, constitutes a valid and reliable measure of the severity of depressive symptoms

[15]. The HAMD scores were obtained at baseline, and 3 days after completing the course of rTMS. Secondary outcome parameters included response and remission rates. For remission, a HAMD score of ≤7 and for response, a decrease in the HAMD total score of at least 50% were accepted.

Beck Depression Inventory

BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression [16]. The BDI demonstrates high internal consistency, with alpha coefficients of .86 and .81 for psychiatric and non-psychiatric populations, respectively [17]. The BDI scores were obtained at baseline and 3 days after completing the course of rTMS.

Brief Psychiatric Rating Scale

Brief Psychiatric Rating Scale (BPRS) is the most established scale for a quick assessment of psychotic and non-psychotic symptoms in individuals with a major psychiatric disorder [18]. Originally, the scale had 16 items; subsequently, 2 items were added, resulting in a 18-item BPRS in 1976. The BPRS was administered at baseline, and 3 days after completing the course of rTMS.

Stroop task

The classic Stroop task involves the presentation of colour words in which participants are asked to name colours printed either congruently (i.e. the word "red" printed in red ink) or incongruently (e.g. the word "red" printed in blue ink) [19]. Participants are asked to name, as quickly as possible, the ink colour of each stimulus word, while attempting to ignore the meaning of the word. This attempt to suppress word meaning in order to name ink colour has reliably been shown to result in longer response latencies than those that result from colour naming congruent stimuli (e.g. the word "red" printed in red ink), a phenomenon that has been referred to as the Stroop effect. Despite the existence of several theories explaining the Stroop effect, it is generally assumed that cognitive processes are open to interference [20]. Stroop task was administered at baseline, and 3 days after completing the course of rTMS.

Trail-making test

TMT ranks among the most frequently used tests in the neuropsychologist's repertoire [21]. Performance on parts A and B of the test involves a variety of cognitive operations and conceptual tracking. The test has been used as a measure of executive cognitive function in a variety of neuropsychiatric and neurologic disorders. TMT was administered at baseline, and 3 days after completing the course of rTMS.

Wisconsin card sorting test

WCST is widely used in psychiatric studies as a quantitative measure of the function of the frontal lobes [22]. The task is to match a series of cards to one of the four target cards varying in colour, shape, and number according to correct/wrong feedback. The WCST proceeded until the subject had completed 6 rating categories or had sorted all 128 cards. The test provides several measures that reflect various aspects of problem-solving behaviour, including the number of trials, the number of categories completed, the number of correct responses, the number of errors, the number of perseverative responses and errors, the number of non-perseverative errors, the number of trials to complete first category, the percentage of conceptual level responses reflecting insight into the correct sorting principles, and failure to maintain the set by making five or more consecutive correct matches but then making an error. WCST was administered at baseline, and 3 days after completing the course of rTMS.

Statistical analyses

Data were analysed using the Statistical Package for Social Sciences (SPSS) software version 19.0 for Windows (SPSS Inc., Chicago, IL). Data are expressed as mean ± SD and statistical significance was assessed within a 95% reliance at a level of $p < .05$ significance. Numeric data and percentages related to patient's features, and prognostic characteristics, necessary cross comparisons were presented as descriptive statistics. A normal distribution of the quantitative data was checked using Kolmogorov–Smirnov and Shapiro–Wilk tests. Parametric tests were applied to data of normal distribution, and non-parametric tests were applied to data of questionably normal distribution. Paired *t*-test and Wilcoxon Signed Ranks test were used to compare dependent groups. Repeated analysis of variance (ANOVA) (Huynh-Feldt) and Friedman tests were used to compare multiple groups. Post hoc analysis was performed by Bonferroni corrected Wilcoxon sign rank and Fishers least significant difference tests. To calculate correlation coefficients, Pearson's *r* was used.

Results

The treatment-resistant depression group included 13 females (68.4%) and 6 males (31.6%), with a mean age of 35.95 ± 10.24 (range 20–57) years. Accompanying systemic disease was present only in one patient (5.3%) as hypertension. The control group included 11 females (55%) and 9 males (45%), with a mean age of 32.47 ± 6.35 (range 27–42) years. The mean education year for depression group was 7.65 ± 5.35 and 9.20 ± 4.45 for the control group. No significant differences were found regarding gender or education level between groups ($p > .05$ for both).

A within-subjects *t*-test showed that the mean HAMD score obtained was significantly different at baseline ($M = 21.58 \pm 6.31$) when compared to the end of rTMS treatment for treatment-resistant depressive patients ($M = 11.00 \pm 8.00$, t (18) = 5,78; $p < .001$). After the treatment period, 10 of 19 patients (52.6%) demonstrated "response" as indexed by a reduction of more than 50% on the HAMD score. Five of these 10 responders (26.3% of study group) attained remission (HAMD score ≤ 7). As for the study group, 9 of 19 patients (47.3%) achieved a partial response. None of the patients had a worsened HAMD score at the end of treatment. Parallel to HAMD findings, there was a significant reduction in mean BDI scores, as well t (18) = 4.36; $p < .001$). The mean BDI scores at baseline and end of the treatment were $M = 24.16 \pm 8.78$ and $M = 13.21 \pm 10.06$, respectively. The mean BPRS score obtained was 23.26 ± 6.56 at baseline, and 10.26 ± 4.82 after completing the course of rTMS (t (18) = 6.35; $p < .001$). For the control group, on the other hand, no significant reduction on HAMD scores was observed at the end of rTMS treatment ($M = 11.00 \pm 6.00$) when compared to baseline scores ($M = 14.00 \pm 4.00$, $p > .05$). BDI and BPRS scores of the control group were not found to be significantly different between baseline ($M = 10.12 \pm 76.98$ for BDI; $M = 8.74 \pm 2.43$ for BPRS) and at the end of rTMS treatment ($M = 11.24 \pm 22.38$ for BDI; $M = 8.12 \pm 6.24$ for BPRS), as well ($p > .05$). The data are shown in Table 1.

A within-subjects *t*-test indicated that the Stroop task score obtained was significantly different between the baseline and following the 20 sessions of rTMS treatment for treatment-resistant depressive group ($M = 48.68 \pm 23.91$, $M = 34.05 \pm 13.46$, respectively, (t (18) = 7,32; $p < .05$)). As for the WCST scores, a repeated ANOVA showed that "correct responses" category increased, and "perseverative errors" category decreased significantly after the treatment (F (1,18) = −4.28; $p < .05$ and F (1,18) = 3.32; $p < .05$, respectively). TMT scores of the patient group did not differ significantly before and after the rTMS treatment ($p > .05$). The control group, however, did not show any significant difference in the Stroop task score between prior to and after the rTMS treatment ($M = 37.68 \pm 45.26$, $M = 38.28 \pm 67.80$, respectively, (t (18) = 1.25; $p > .05$). The WCST and TMT scores did not differ at the end of rTMS treatment as well ($p > .05$ for both).

Table 1. The mean clinical evaluation scores for HAMD, BDI, and BPRS before and after the treatment.

		Baseline scores (Mean ± SD)	Post-treatment scores Mean ± SD)
Treatment-resistant depression group	HAMD	21.58 ± 6.31	11.00 ± 8.00
	BDI	24.16 ± 8.78	13.21 ± 10.06
	BPRS	23.26 ± 6.56	10.26 ± 4.82
Control group	HAMD	14.00 ± 4.00	11.00 ± 6.00
	BDI	10.12 ± 76.98	11.24 ± 22.38
	BPRS	8.74 ± 2.43	8.12 ± 6.24

Baseline BDI, HAMD, and Stroop task scores were subtracted from post-treatment scores so as to check the correlation between the amelioration in executive functions and the reduction in depressive symptoms for the treatment-resistant depression group. As expected, the Pearson's correlation coefficient between the change in mean BDI scores and Stroop task score before and after the treatment was positive and significant at .75 level, $p < .05$. Similarly, the Pearson's correlation coefficient between the change in mean HAMD scores and Stroop task score before and after the treatment was positive and significant at .69 level, $p < .05$. On the other hand, correlation analyses between depression scales and other cognitive tests were not found to be statistically significant, $p > .05$.

In our study group, the magnetic stimulation was generally well tolerated. Side effects such as seizure, cognitive difficulties, seizures, headache, tinnitus, dizziness, or nausea which observed during rTMS studies in the literature were not observed.

Discussion

The main outcome of the study was that the 25 Hz high-frequency rTMS treatment did not lead to any deterioration on executive functions and even improved some scores of certain cognitive tests. Besides, the significant reduction of baseline depression scores indicating improvement of depressive symptoms following the rTMS was another important finding of the study. Our results are in agreement with the findings of previous studies suggesting that daily 25-Hz high-frequency rTMS is well tolerated and found to be effective in patients with treatment-resistant depression and have benefits on cognitive functions [23,24].

In the present study, although BDI, BPRS, and Stroop task scores differed significantly after the rTMS treatment, TMT scores did not change, and WCST scores only differed in two categories, "correct responses" and "perseverative errors". Several studies using the WCST revealed contradictory results. Successful performance in the test requires a complex set of cognitive functions, including the ability of abstract thinking, selectively attending to a particular perceptual dimension, and cognitive set shifting. It is not entirely clear, however, which of these functions are disturbed during episodes of depression. Furthermore, it is not yet clear whether the observed deficit reflects localized dysfunction of the prefrontal cortex or a more generalized impairment affecting multiple brain regions. In the present study, "correct responses" category increased, and "perseverative errors" category decreased significantly after the treatment.

The therapeutic role of repetitive rTMS is based on its ability to differentially modulate neural activity depending on stimulation parameters such as

location, frequency, coil type, pulse waveform, or current direction [25,26]. Motor cortex studies suggest that high- and low-frequency rTMS have opposite effects on the excitability of neurons in brain cortex [27]. In a systematic review by Guse et al. [24], they reported that in comparison with studies using 1-Hz stimulation, high-frequency studies seem to be superior regarding the cognitive outcome [24]. They stated that high-frequency rTMS (10–20 Hz) is most likely to cause significant cognitive improvement when applied over the left prefrontal cortex, within a range of 10–15 successive sessions and an individual motor threshold between 80% and 110%. As the effects of rTMS depend on the stimulation pattern, in our study, rTMS with 25 Hz seems to increase the effectiveness of rTMS protocol. Imaging studies have shown evidence for reduced blood flow in the left prefrontal cortex in depressed patients [26]. There is considerable evidence from neuropsychological, lesion and imaging studies showing that the left and right hemispheres have contrasting roles in mood regulation and part of cognition also [28]. A recent study demonstrated that high-frequency rTMS over the left DLPFC has an enhancing effect on Stroop task performance in healthy participants [29]. Similar results were obtained in another study on patients with drug-resistant major depression, and high-frequency rTMS over the left DLPFC was found to increase Stroop task performance for short term [30]. However, a meta-analysis including 18 studies showed that the rTMS treatment to prefrontal cortex in patients with depression had no effect on cognitive functioning except TMT performance [31].

One key aspect of our study is that we assessed the effectiveness of rTMS in drug-free treatment-resistant depression patients. The use of rTMS as an additional strategy in conjunction with antidepressant drug treatment resulted in a great improvement but we found a comparable ratio of remission with rTMS-only treatment in treatment-resistant patients.

Previous studies reported that the interval between stimulation and follow-up testing is important, as well. It has been shown that rTMS can produce changes in regional cerebral blood flow that persist for at least 3 days [32]. So in our study, psychiatric and neuropsychological assessments were conducted 3 days after stimulation. One of limitations in this study is a lack of information about the effects of long-term rTMS on cognition.

The most common side effects of rTMS are pain or discomfort during stimulation. In the study by Su et al. [33], 3 of 30 patients were dropped out of the treatment because of pain or worsening of clinical symptoms [33]. In an rTMS study in the geriatric population, Hizli Sayar et al. [34] reported that the magnetic stimulation was generally well tolerated [34]. Cognitive difficulties, seizures, headache, tinnitus, dizziness, or nausea observed in rTMS studies in the literature were not observed in our study group. None of the patients withdrew from the study or reported serious adverse effects.

The main limitation of this study was the small study group, which likely restricted the statistical power. Also, it is known that any remedial effects of treatment can potentially arise from two sources: one related to the specific properties of treatment and the other associated with the patient's expectations for the treatment (placebo effect). The magnitude of the placebo effect varies according to its supposed effectiveness and emotional impact on the treated subject. Many studies reported response rates for patients who received placebo treatment. Klein et al. [35] reported a control group response rate as high as 25% [35]. Patients receiving placebo rTMS may receive a small dose of magnetic energy that may alter their depression. However, we tried to exclude this effect compared to the control group.

The significantly improved scores on the Stroop test and some parts of WCST, but not in TMT may be explained due to practice and learning effect on WCST. Also, improvement in cognitive performance might be associated with improvement in depressive symptoms. The duration of the improving effects of rTMS on cognitive function is not known. But one can assume, based on the observation of remaining effects on depressive symptoms, that the cognitive improvement will also persist for a certain period of time. It is well known that state of depression can be rapidly altered depending on a various drug therapies, even with a single course of ECT. As the literature consists of numerous studies in which HAMD and BDI scores are regarded as the marker of the effect of the treatment and severity of depression both in short-term and long-term treatments, we suggest that learning effect on depression scores is not as valid as it is on cognitive tasks.

Conclusion

In conclusion, 25-Hz high-frequency rTMS is safe and well tolerated in drug-free treatment-resistant depressed patients. This study contributed to the existing evidence of the antidepressant effect of rTMS therapy. Results of this study suggest that rTMS does not have negative effects on executive functions, and some have revealed post-stimulation improvement in a range of neuropsychological domains including executive functioning. Despite the fact that the generalizability of our study findings is limited, the 25-Hz high-frequency rTMS treatment in treatment-resistant depressed population is showing encouraging results. Future investigations are needed to assess cognitive effects of rTMS in different psychiatric disorders versus healthy subjects.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol. 2003;2:145–156.

[2] Peterchev AV, Wagner TA, Miranda PC, et al. Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. Brain Stimul. 2012;5:435–453.

[3] George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry. 2013;26:13–18.

[4] Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci. 2003;7:415–423.

[5] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Neuroscience. 2002;3:201–215.

[6] Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol. 2001;112:1367–1377.

[7] Slotema CW, Blom JD, Hoek HW, et al. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? J Clin Psychiatry. 2010;71:873–884.

[8] George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010;67:507–516.

[9] Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatricdisorders? Neuropharmacology. 2013;64:566–578.

[10] Ahmed MA, Darwish ES, Khedr EM, et al. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. J Neurol. 2012;259:83–92.

[11] Kim SH, Han HJ, Ahn HM, et al. Effects of five daily high-frequency rTMS on Stroop task performance in aging individuals. Neurosci Res. 2012;74:256–60.

[12] Moser DJ, Jorge RE, Manes F, et al. Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology. 2002;58:1288–1290.

[13] Boggio PS, Fregni F, Bermpohl F, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. Mov Disord. 2005;20:1178–1184.

[14] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.

[15] Akdemir A, Orsel S, Dag I, et al. [Hamilton depresyon derecelendirme ölçeğinin geçerliliği. güvenilirliği ve klinikte kullanımı.] [Hamilton Depression Rating Scale (HDRS) and its validity, reliability and clinical use] [Turkish]. Psikiyatri Psikoloji Psikofarmakoloji Dergisi. 1996;4:251–259.

[16] Beck, A, Ward, C, Mendelson, M, et al. (1961). An inventory for measuring depression. Arch Gen Psychiatry. 1961:4;561–571.

[17] Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psychol Rev. 1988;8:77–100.

[18] Overall JE, Gorham D. The Brief Psychiatric Rating Scale. Psychol Rep. 1962;10:799–812.

[19] Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18:643–662.

[20] MacLeod CM. Half a century of research on the Stroop effect: an integrative review. Psychol Bull. 1991;109:163–203.

[21] Partington JE, Letter RG. Partington's pathway test. Psychol Serv Cent Bull. 1949;1:9–20.

[22] Berg EA. A simple objective test for measuring flexibility in thinking. J Gen Psychol. 1948;39:15–22.

[23] Tarhan N, Hızlı FG, Tan O, et al. Efficacy of high-frequency repetitive transcranial magnetic stimulation in treatment-resistant depression. Clin EEG Neurosci. 2012;43:279–84.

[24] Guse B, Falkai P, Wobrock T. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. J Neural Transm. 2010;117:105–122.

[25] Valero-Cabré A, Payne BR, Pascual-Leone A. Opposite impact on (14)C-2-deoxyglucose brain metabolism following patterns of high and low frequency repetitive transcranial magnetic stimulation in the posterior parietal cortex. Exp Brain Res. 2007;176:603–615.

[26] Paus T, Barett J. Transcranial magnetic stimulation (TMS) of the human frontal cortex: implications for repetitive TMS treatment of depression. Rev Psychiatr Neurosci. 2004;29:268–279.

[27] Pascual-Leone A, Valls-Sole J, Wassermann EM, et al. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain. 1994;117:847–858.

[28] Silberman E, Weingartner H. Hemispheric lateralization of functions related to emotion. Brain Cogn. 1987;5:322–353.

[29] Yanmin L, Lin W, Meng J, et al. The effects of high-frequency rTMS over the left DLPFC on cognitive control in young healthy participants. PLoS One. 2017;12:e0179430.

[30] Donel MM, Shawn M, Jane JF. Cognitive enhancing effects of rTMS administered to the prefrontal cortex in patients with depression: A systematic review and meta-analysis of individual task effects. Depress Anxiety. 2017;34:1029–1039.

[31] Concerto C, Lanza G, Cantone M, et al. Repetitive transcranial magnetic stimulation in patients with drug-resistant major depression: A six-month clinical follow-up study. Int J Psychiatry Clin Pract. 2015;19:252–258.

[32] Speer AM, Kimbrell TA, Wasserman EM, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry. 2000;48:1133–1141.

[33] Su TP, Huang CC, Wei IH. Add-On rTMS for medication-resistant depression: a randomized, double blind, sham-controlled trial in Chinese patients. J Clin Psychiatry. 2005;66:930–937.

[34] Hizli Sayar G, Ozten E, Tan O, et al. Transcranial magnetic stimulation for treating depression in elderly patients. Neuropsychiatr Dis Treat. 2013;9:501–504.

[35] Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. Arch. Gen. Psychiatry. 1999;56:315–320.