Effect of Repetitive Transcranial Magnetic Stimulation on Meta-Worry and Neuropsychological Functions among Patients with Depression

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Abstract
Background: Repetitive transcranial magnetic stimulation (rTMS) is recommended as an effective treatment for both major depressive disorder (MDD) and treatment-resistant depression.

Objectives: According to the possible impact of rTMS on cognitive psychological characteristics, this study aimed to determine the effectiveness of rTMS in meta-worry and neuropsychological functions among MDD patients.

Methods: This quasi-experimental study was conducted on 30 patients with MDD referring to Atieh Clinical Neuroscience Center, Tehran, Iran, in 2019. The participants were randomly divided into two groups of intervention and control (n=15 each). The data collection tools included the Beck Depression Inventory, meta-worry subscale of the Anxious Thoughts Inventory, and Cambridge Neuropsychological Test Automated Battery.

Results: The comparison between the two groups showed that the scores of the meta-worry scale improved after the intervention in patients undergoing rTMS, compared to those in the control group (Z= 3.41; P<0.002); however, no difference was observed between the two groups in the follow-up (Z= 2.02; P=0.053). The assessment of neuropsychological functions among the patients undergoing rTMS and those in the control demonstrated that neuropsychological functions (i.e., Minimum Spanning Tree, Rapid Visual Information Processing, and Spatial Working Memory) were significantly different immediately after the intervention and in the follow-up (P<0.05) except for the Difficulty Maintaining Sleep (DMS) subtest. In addition, the mean depression score was significantly different between the two groups (Z= 4.17; P<0.005). There was a significant relationship between depression and all the subtests of neuropsychological functions except for DMS (P>0.05).

Conclusion: In summary, the results of the current study indicated that the use of rTMS was an effective method in the improvement of neuropsychological functions except for DMS in patients with depression. However, the obtained findings did not demonstrate the persistent effect of multiple rTMS on meta-worry.

Keywords: Depression, Meta-worry, Neuropsychological functions, Transcranial magnetic stimulation

1. Background

Depression is the most common mental disorder after anxiety and is associated with several symptoms, including a lack of motivation, loss of appetite, decreased social functioning, sleep disorders, and isolation (1). The prevalence rate of depression is reported within the range of 5-17% around the world (2) and estimated at 25% in Iran (3). Currently, due to the abundance of etiological factors, such as social status, abnormal lifestyle, economic status, environmental stress, and chronic diseases, this disorder has become highly prevalent (4).

One of the issues that patients suffering from depression deal with is meta-worry. The beliefs and negative evaluations of anxiety, such as worrying about anxiety, are called meta-worry. Meta-worry involves the beliefs about the positive and negative effects of worry. It plays the main role in the development and maintenance of generalized anxiety disorder (5). Another problem of patients with depression is related to their neuropsychological functions (6). Working memory is highly important for many higher-level cognitive functions, such as problem-solving, reasoning, planning, and behavior guiding. These functions are affected in patients suffering from depression with problems of neuropsychological functions (7).

Antidepressants are the first-line treatments adopted for mood disorders, especially depression. In addition, electroconvulsive therapy (ECT) is performed only for patients who do not respond to medication or are intolerant to medication (8). However, response to antidepressants is variable; accordingly, fewer than half of depressed patients respond to their first drug treatment, leading to the prolongation of treatment time and an increase in medical costs (9). Psychotherapy and ECT are suggested as viable options for the treatment of non-responders with major depressive disorder (MDD) (10). However, the application of the aforementioned approaches is involved with several problems, such

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as treatment discontinuation due to the long duration of psychotherapeutic treatments and possible risks of ECT (11), which are performed only for patients who do not respond to medication or are intolerant to medication (12).

In general, more than a third of patients with treatment-resistant depression (TRD) continue to suffer from residual symptoms (13, 14). Treatment-resistant depression is a multiple risk factor and complex clinical problem, which should be targeted by integrated therapeutic strategies (e.g., the optimization of medications and psychosocial and cultural therapies) and somatic therapies (e.g., ECT, repetitive transcranial magnetic stimulation [rTMS], and deep brain stimulation) (13). In this regard, rTMS is recommended by the Food and Drug Administration for the treatment of both MDD and TRD. Transcranial magnetic stimulation acts on the brain areas involved in the pathogenesis of MDD (15). It is a non-invasive and safe procedure affecting the cortical activity of the stimulated area by sending electric currents that modify the glucose levels and activity of neurotransmitters in that area (16).

The results of some studies showed that rTMS is effective in the treatment of triple signs and symptoms of depression (i.e., cognition, body, and negative-worthlessness). The rTMS affected the left posterior cortex, which improved the neuropsychological function of patients with depression (17). Pirmoradi et al. observed that multiple TMS reduced cognitive and physical symptoms, pessimism, and feelings of worthlessness in patients with depression (18). According to another study performed by Durnaz et al., multiple rTMS decreased the symptoms of depression and anxiety (19). The effectiveness of multiple magnetic stimulations of the brain in working memory and depression is also confirmed by some studies (20, 21).

Although the effectiveness of rTMS in the cognitive function of patients with depression is widely evaluated, a limited number of studies assessed the effect of rTMS on meta-worry, as the main issue patients suffering from depression are dealing with. Meta-worry is a part of the metacognitive model which has been studied in patients with obsessive-compulsive disorder (22). It seems that there is a relationship between meta-worry and neurocognitive abilities in patients suffering from depression. The findings of functional neuroimaging studies showed a decrease in the activity of the left prefrontal cortex, especially in Brodmann areas (i.e., BA9 and BA46), in depressed patients. Moreover, pieces of evidence have been indicative of the activation changes in the cortico-subcortical network (i.e., subgenual and anterior cingulate cortices) among the patients (23). However, a heterogeneous neuropsychological performance was reported among depressed patients; therefore, it is necessary to consider the differences between patients in terms of cognitive deficits (24).

The investigation of treatment methods in patients with financial depression is of great importance due to the high prevalence of depression, cognitive psychological problems of the patients, and impact of depression on the quality of life.

2. Objectives

According to the possible effect of rTMS on the cognitive psychological characteristics of patients and inadequacy of performed studies on the effects of the above-mentioned treatments on meta-worry and neuropsychological functions, this study was conducted to determine the effectiveness of rTMS in meta-worry and neuropsychological functions among patients with depression.

3. Methods

This quasi-experimental study was conducted on a total of 30 patients with MDD referring to Atieh Clinical Neuroscience Center in Tehran, Iran, in 2019.

3.1. Inclusion and Exclusion Criteria

Patients with a definite diagnosis of MDD (score of ≥20 based on the Beck Depression Inventory), the age range of 20-50 years, and junior high school education or higher were entered into this study. Moreover, the eligible patients had no history of mindfulness-based cognitive therapy or stressful events, such as death and divorce in the past 3 months. The exclusion criteria were pregnancy, history of concussion or seizures in the family, bipolar disorder, psychotic disorders, psychotropic or substance abuse, and metal implant/prosthesis or heart rate induction device. In addition, patients with a comorbid neurological or psychiatric diagnosis were excluded from the study. The absence of more than one session and incomplete questionnaires were also other exclusion criteria.

3.2. Research tools

3.2.1. Beck Depression Inventory

This 21-item questionnaire is scored on a 4-point Likert scale (0-3). The total score of the questionnaire is calculated based on the sum of the scores of the items, rendering for the range of 0-63, with higher scores indicating higher levels of depression. In this tool, the score ranges of 0-10, 11-16, 17-20, 21-30, 31-40, and > 40 are respectively considered normal, slight, mild, moderate, severe, and very severe depression. The predictive validity of this instrument was confirmed in Iran, and its reliability was estimated at 0.89 by Cronbach’s alpha coefficient (18).

3.2.2. Meta-worry subscale

This 7-item questionnaire is used for the assessment of anxiety level and is scored on a 4-point
Iran used to stimulate the dorsolateral prefrontal cortex (DLPFC). Magnetic Stimulator (Neurosoft, Ivanovo, Russia) was utilized for the intervention, Neurosoft Transcranial Magnetic Stimulator (Neurosoft, Ivanovo, Russia) was used to stimulate the dorsolateral prefrontal cortex by creating magnetic fields (i.e., bilaterally over the dorsolateral prefrontal cortex). Electric currents, after passing through the coil that is placed on the head of the patient, generate magnetic fields leading to a lighter electric current in the cerebral cortex which stimulates the target nerve tissue. Each of the two stimuli had a frequency and intensity of 10 Hz and 120% motor threshold, respectively, and lasted for 5 sec with a 10-second interval. This mechanism was performed on the posterior cortex of the left forehead for 5 weeks and four 30-minute sessions each week. The rTMS on the dorsolateral prefrontal cortex was performed by a specialist in Atieh Clinical Neuroscience Center, Tehran, Iran.

The required data were collected using a demographic characteristic form, including gender, age, and educational level. Moreover, the Beck Depression Inventory, a meta-worry subscale of the Beck Depression Inventory, a meta-worry subscale of the Anxious Thoughts Inventory, and Neuropsychological Function Test were employed as other tools to gather the required data. The patients were assessed in terms of depression, meta-worry, and neuropsychological functions before the intervention and immediately and 3 months after the intervention.

3.4. Statistical Analysis
The collected data were analyzed in SPSS software (version 23) using the Shapiro-Wilk test (to assess the normality of the data), Levene’s test (to measure the homogeneity of variance and covariance), and Mauchly’s test of sphericity (to calculate the homogeneity of covariance). Independent t-tests, paired t-test, and analysis of variance were also utilized for quantitative variables. Additionally, the Chi-square test was employed for qualitative variables. A p-value of less than 0.05 was considered significant.

3.5. Ethical considerations
This article was derived from a thesis submitted for the partial fulfillment of the requirement for a PhD in clinical psychology to Shahid Beheshti University of Medical Sciences, Tehran, Iran, and Health Services in Tehran. The protocol of the present study was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences. This study was conducted according to the Helsinki Human Rights criteria (ethics code of IR.SBMU.MSP.REC.1397.95). Before the initiation of the study, the objectives were explained to the patients, and informed consent was obtained from all the study participants. The patients were assured that their information would remain confidential and they could withdraw from the study at any time.

4. Results
A total of 30 patients were selected and divided into the intervention and control groups. It should be
mentioned that there was no sample attrition. The age mean values of the subjects in the intervention and control groups were obtained at 37.6±95.29 and 37.11±6.48 years, respectively. Table 1 tabulates the comparison of demographic characteristics, indicating no significant difference between the studied groups in terms of age, gender, and educational level (P>0.05). In addition, the mean scores of depression before and after the intervention were estimated at 29.3 and 19.4, respectively. The comparison of depression scores after the intervention showed a significant difference between the two groups (Z=-4.17; P<0.005).

Table 1. Frequency of demographic characteristics among the participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Intervention</th>
<th>Control</th>
<th>Total</th>
<th>χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>0.61</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10</td>
<td>6.67</td>
<td>20</td>
<td>6.67</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>21-30</td>
<td>3</td>
<td>20.0</td>
<td>5</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31-40</td>
<td>5</td>
<td>33.3</td>
<td>12</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>7</td>
<td>46.7</td>
<td>13</td>
<td>43.3</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td>High school</td>
<td>1</td>
<td>6.67</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associate degree</td>
<td>5</td>
<td>33.3</td>
<td>9</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bachelor’s degree</td>
<td>6</td>
<td>40</td>
<td>11</td>
<td>36.7</td>
<td></td>
</tr>
</tbody>
</table>

The comparison between the two groups at the baseline, indicating the significant difference in the meta comparison of the meta variables (P<0.05). Therefore, it can be said that the difference between the mean score of variables in the different stages of the study was significant. Table 4 tabulates the comparison of the baseline stage with the post-treatment and follow-up stages based on the Bonferroni test. Regarding, the mean value of the baseline stage had a significant difference with those reported for the post-treatment and follow-up stages regarding the meta-worry and neuropsychological function variables (P<0.05). However, the difference between the mean values of the post-treatment and follow-up stages was not significant for any of the variables (P>0.05). In other words, multiple TMS significantly reduced meta-worry and improved neuropsychological functions in patients with depression in the post-treatment and follow-up stages, compared to those reported for the baseline stage.

Table 2. Comparison of meta-worry and neuropsychological functions in patients with major depressive disorder

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Statistical test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Standard deviation</td>
<td>Mean</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>Meta-worry</td>
<td>Baseline</td>
<td>11</td>
<td>5.34</td>
<td>13.13</td>
<td>4.22</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>6.86</td>
<td>3.97</td>
<td>12.13</td>
<td>4.45</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>8.66</td>
<td>3.9</td>
<td>11.6</td>
<td>4.03</td>
</tr>
<tr>
<td>Motor</td>
<td>Baseline</td>
<td>50.93</td>
<td>5.18</td>
<td>49.8</td>
<td>3.52</td>
</tr>
<tr>
<td>Screening</td>
<td>Post-treatment</td>
<td>65.73</td>
<td>10.13</td>
<td>52.6</td>
<td>5.52</td>
</tr>
<tr>
<td>Task</td>
<td>Follow-up</td>
<td>62.86</td>
<td>8.95</td>
<td>53.46</td>
<td>4.68</td>
</tr>
<tr>
<td>Rapid Visual Information Processing</td>
<td>Baseline</td>
<td>49.46</td>
<td>4.307</td>
<td>51.2</td>
<td>3.72</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>56.73</td>
<td>3.88</td>
<td>51</td>
<td>3.52</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>56.06</td>
<td>3.88</td>
<td>50.66</td>
<td>3.71</td>
</tr>
<tr>
<td>Spatial</td>
<td>Baseline</td>
<td>51</td>
<td>5.73</td>
<td>50.8</td>
<td>6.81</td>
</tr>
<tr>
<td>Working</td>
<td>Post-treatment</td>
<td>58.66</td>
<td>6.46</td>
<td>50.73</td>
<td>7.15</td>
</tr>
<tr>
<td>Memory</td>
<td>Follow-up</td>
<td>57.33</td>
<td>9.54</td>
<td>46.26</td>
<td>5.13</td>
</tr>
<tr>
<td>Delayed</td>
<td>Baseline</td>
<td>50.4</td>
<td>5.56</td>
<td>49.93</td>
<td>6.54</td>
</tr>
<tr>
<td>Matching to Sample</td>
<td>Post-treatment</td>
<td>56.2</td>
<td>9.19</td>
<td>50.26</td>
<td>8.26</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>55.66</td>
<td>7.84</td>
<td>50.73</td>
<td>8.87</td>
</tr>
</tbody>
</table>
No significant difference was observed between the post-treatment and follow-up stages in terms of any of the variables. The significant difference between the baseline and post-treatment stages indicated the effect of the intervention. Moreover, the significant difference between the baseline and follow-up stages suggested the maintenance of the influence of the intervention on the follow-up phase. Table 5 presents the correlation between depression and neuropsychological functions. Based on the obtained results, there was a significant relationship between depression and all the subtests of neuropsychological functions after the intervention except for DMS (P>0.05).

Table 5. Correlation between depression with meta-worry and neuropsychological functions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Depression</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-worry</td>
<td>Post-treatment</td>
<td>0.67</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Motor Screening Task</td>
<td>Post-treatment</td>
<td>-0.52</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Rapid Visual Information Processing</td>
<td>Post-treatment</td>
<td>-0.35</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Spatial Working Memory</td>
<td>Post-treatment</td>
<td>-0.35</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>Delayed Matching to Sample</td>
<td>Post-treatment</td>
<td>-0.04</td>
<td>0.802</td>
<td></td>
</tr>
</tbody>
</table>

5. Discussion

In summary, considering the results of correlation analysis between possible changes in depression scores and changes in meta-worry and cognitive measurements, the improvements in neuropsychological functioning (and meta-worry) were associated with the improvements in depression. The scores of the meta-worry scale improved after the intervention in the patients undergoing rTMS than those in the control group; however, the obtained data did not confirm the persistent effect of rTMS on meta-worry in MDD patients. Additionally, rTMS enhanced neuropsychological functions (i.e., MST,
noticed that potentiation mechanism of cortical stimulation, along with memory improvement, hypothesis of learning and memory. Non-accepted model of neural flexibility as the strong synaptic activity. This mechanism is a widely continuous synaptic transmission resulting from this long meta-stage. The aforementioned results are consistent with the findings of the previous studies in this regard (17-19, 28). Similarly, the results of a study performed by Cirillo et al. showed that TMS could reduce meta-worry (25). Durmaz et al. reported that multiple rTMS decreased anxiety symptoms (19).

It is suggested that multiple rTMS be considered a new technique for the treatment of depression. In this method, the magnetic field allows the depolarization of cortical nerve cells by sending pulses to the skull. In addition, different from electrical stimulation, TMS allows focal brain stimulation in any area and does not require anesthesia or lead to complications, such as long-term cognitive issues. Since this method stimulates the brain, it has long-term effects that can reduce meta-worry in patients with depression, which is indicative of the positive effects of this treatment (29, 30).

According to the results of the present study, multiple rTMS improved the neuropsychological functions of patients with depression in the post-treatment and follow-up stages. However, no significant difference was observed between the subjects' neuropsychological functions in the post-treatment and follow-up stages, which is consistent with the results of previous studies (27, 31). The findings of a study conducted by Rahimi et al. revealed the effect of multiple TMS of the left posterior cortex on the improvement of neuropsychological functions in patients with depression (17). Taherifard et al. demonstrated that transcranial direct-current stimulation enhanced cognitive functions, such as short-term memory, visual-spatial skills, executive functions, attention, concentration, working memory, language, and awareness of time and space (28).

In another study, Vanderhasselt et al. showed that multiple TMS improved the working memory of patients with depression (21). Based on the findings of a study carried out by Ashaghhi et al., the reduction of meta-worry by multiple TMS could be attributed to its long-term potentiation mechanism and a strong continuous synaptic transmission resulting from this strong synaptic activity. This mechanism is a widely accepted model of neural flexibility as the underlying hypothesis of learning and memory. Non-invasive cortical stimulation, along with memory improvement, facilitates the increase in the effects of the long-term potentiation mechanism (27).

Many psychological disorders in patients with mood disorders improve after a variety of therapeutic interventions. However, it should be noticed that multiple TMS independently enhances various aspects of neuropsychological functions. This stimulation affected neuropsychological functions due to the high number of pulses used in the current study, compared to those in the previous studies. The intensity of stimulation can also be an effective factor. Furthermore, when the mean age of the patient increases, high-intensity stimulation is usually used to compensate for cerebral atrophy.

5.1. Limitations and Recommendations

The most important limitations of this study included the use of the convenience sampling method, relatively small sample size, lack of comparison of the results regarding the gender, and use of self-reporting tools for the diagnosis of depression. Another limitation was related to the lack of any other intervention method to compare its effects with those of the multiple TMS. Consequently, it is recommended to carry out further studies to use the random sampling method, consider a larger sample size for each group, compare the results based on gender, and use semi-structured interviews for the assessment of depression. Furthermore, the effect of multiple TMS on other cognitive psychological variables, such as rumination, should also be investigated and compared to those reported for other treatment methods, including neurofeedback. In addition, it is suggested that therapists use multiple TMS for health-related interventions, along with other treatments, especially for the reduction of meta-worry and improvement of neuropsychological functions in patients with depression.

6. Conclusion

In conclusion, the results of the present study indicated that the use of multiple rTMS was effective for the improvement of neuropsychological functions except for the DMS in patients with depression. However, the obtained findings did not demonstrate the persistent effect of multiple rTMS on meta-worry. Furthermore, the results confirmed the relationship between depression with meta-worry and neuropsychological functions.

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Footnotes

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44. Rahimi M. The effects of repetitive transcranial magnetic stimulation (rTMS) over the left DLPFC on neuropsychological