REVIEW ARTICLE

Repetitive Transcranial Magnetic Stimulation in Psychiatric Disorders: A Review of Clinical Advances

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Abstract

Psychiatric disorders are the most common debilitating diseases worldwide. Repetitive transcranial magnetic stimulation (rTMS) has shown therapeutic outcomes in different neurophysiology and neuropsychiatric disorders. Despite controversial findings on the therapeutic outcomes of this technique in different psychiatric disorders, researchers emphasize on developing this technique as an alternative or adjunctive modality for these disorders. Depression, different hallucinations, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and substance abuse are the main disorders have shown good treatment response to rTMS. This study aims to comprehensively overview the applications and recent advances in rTMS applications in psychiatric disorders. The databases of PubMed (1985-2017), Web of Sciences (1985-2017), Embase (1985-2017), Cochrane Central Library (1985-2017), and Google Scholar (1985-2017) were searched using the keywords of repetitive transcranial magnetic stimulation OR rTMS AND psychiatric disorders AND treatment. The retrieved records were reviewed, and the relevant studies were selected for further review. Repeated sessions of low frequency (≤5 Hz) rTMS induce long-lasting neural inhibition or depotentiation, whereas high frequency (>5 Hz) induces long-lasting neural excitability or potentiation. Depending on the neural alteration induced by a disorder, low- or high-frequency rTMS is used for the treatment. The rTMS is approved as acute treatment for major depression. The other diseases with promising outcomes are different hallucinations, OCD, and PTSD. rTMS seems to be an alternative or adjunctive therapeutic modality in different psychiatric disorders. To reach efficient clinical application for each disorder, further randomized clinical trials, as well as preclinical studies, are needed.

Key words: Psychiatric disorders, repetitive transcranial magnetic stimulation, treatment

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive, safe and relatively painless modality that has been used to study different cognitive functions as well as to determine the brain–behavior relationships in normal individuals as well as in various neuropsychiatric disorders. The rTMS modality has recently received a plenty of research interests as a new therapeutic modality in different disorders as well as enhancing cognitive functions among healthy subjects. The main advantages of the modality that have made it an appropriate candidate for various conditions are non-invasiveness, safety, easy handling, and no significant side effects. It has been suggested that effects of rTMS are due to the rTMS-induced modulation of cortical excitability.[1] This technique stimulates neurons with rapidly changing magnetic pulses which can lead to physiological and neurocognitive alterations in the brain. The induced effects can last some minutes to several days with potential applications for the treatment of different disorders. Several neuroimaging studies have demonstrated that single or repeated sessions of rTMS can activate the underlying brain region as well as distinct regions. Several studies have shown that depending the frequency of rTMS; the neurophysiological effects can be divided into inhibitory or excitatory effects. The 10 Hz rTMS to the left dorsolateral

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prefrontal cortex (DLPFC) increases blood flow, whereas 1 Hz stimulation decreased blood flow. Different protocols of rTMS have demonstrated therapeutic efficacies for various neuropsychiatric disorders such as depression, Parkinson's disease, dystonia, mania, tinnitus, and substance abuse.[2-7] Despite controversial findings on the therapeutic outcomes of this technique in different psychiatric disorders, researchers emphasize on developing this technique as an alternative or adjunctive modality for these disorders. Depression, different hallucinations, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), migraine tinnitus, substance abuse, and the main disorders have shown good treatment response to rTMS.[8] This study aims to comprehensively overview the applications and recent advances in rTMS applications in psychiatric disorders.

METHODS

The databases of PubMed (1985-2017), Web of Science (1985-2017), Embase (19850-2017), Cochrane Central Library (1985-2017), and Google Scholar were searched using the set keywords. The keywords were "transcranial magnetic stimulation" OR "TMS" OR "repetitive transcranial magnetic stimulation" OR "rTMS" AND "psychiatric disorders" AND "treatment." The obtained records were reviewed for the abstract by two authors to select the relevant records for full review. Then, a consensus decision was made whether the study is relevant for the full review. Human studies that evaluate the effects of rTMS in any psychiatric disorders and measures at least one psychometric or objective measure were included for further review.

Search strategy

The scientific records were retrieved by a systematic search of different bibliographic databases, and the last update of the search was performed on February 20, 2017. The databases of PubMed, Web of Science, Embase, Cochrane Central Library, and Google Scholar were used. The language of search was limited to English. The search keywords based on the MeSH heading included "transcranial magnetic stimulation" OR "TMS" OR "repetitive transcranial magnetic stimulation" OR "rTMS" AND "psychiatric disorders" AND "treatment." The titles and abstracts of all the records retrieved by the search strategy were reviewed by two authors, and the relevant records with full-texts available were selected for full review. Moreover, the reference lists of the relevant papers were checked manually to identify additional eligible studies. These papers were also included for the full review.

Inclusion and exclusion criteria

The screening and identification of the records for inclusion or exclusion were performed independently by the two reviewers and disagreements were resolved by discussion. Only randomized clinical trials were eligible if they fulfill the following conditions: Human studies evaluating the effects of rTMS in healthy individuals on attention function. Studies were excluded if (a) Abstract only, (b) letter to editor, (c) editorial, (d) conference papers, (e) pilot study, (f) case reports, (g) animal models, and (h) studies with no control or placebo stimulation. The flowchart of the study process is presented in Figure 1.

RESULTS

The searches initially identified 147 records. After reviewing the abstract of each record, 35 cases were excluded because of duplication or irrelevance. During the screening stage, 24 records consisting of 3 abstract only, 5 case reports, 2 books, 2 letters to editor, 4 editorials, 5 conference papers, and 3 pilot studies were excluded from the study. Of 88 records reviewed for eligibility, 14 studies were excluded as they were not on human subjects or with no control or placebo stimulations. Two studies were added from the references of the retrieved records and total of 76 studies were fully reviewed. Because of the immense amount of studies, different methodologies and treatment protocols, the present study aims to provide a comprehensive and descriptive overview of rTMS applications in psychiatric disorders and review the therapeutic efficacies of the technique in each disorder.

rTMS in depression

Depression is one of the most common psychiatric disorders worldwide and by 2020, it will be the second cause of disability, after heart ischemic disease.[9] At present, the standard treatment options for depressive disorder are drug therapy, psychotherapy, drug therapy plus psychotherapy, and electroconvulsive therapy.[10,11] Despite using various antidepressant drugs, a significant portion of the patients suffers drug-resistant depression.[12] Therefore, several non-medication techniques have been developed for the treatment of depression including neurofeedback and biofeedback, transcranial direct current stimulation, vagus nerve stimulation, and rTMS.[10,13-15] Neuroimaging and neurophysiological studies on the brain of depressed patients have indicated that certain regions of the brain are involved in depression development such asDLPFC, subgenual cingulate gyrus, and limbic nucleus.[16-18] In this regard, the metabolic activities of specific regions of the brain are modulated in depression.[19] PET studies in depression have shown dysfunction of serotonin hormone receptors[17] and disturbance of glucose local metabolism in prefrontal cortex.[18] Furthermore, in addition to the metabolic and physiological variables, electrical and magnetic activities of different brain regions are disturbed during the depression. This is expectable as there is mutual relationship

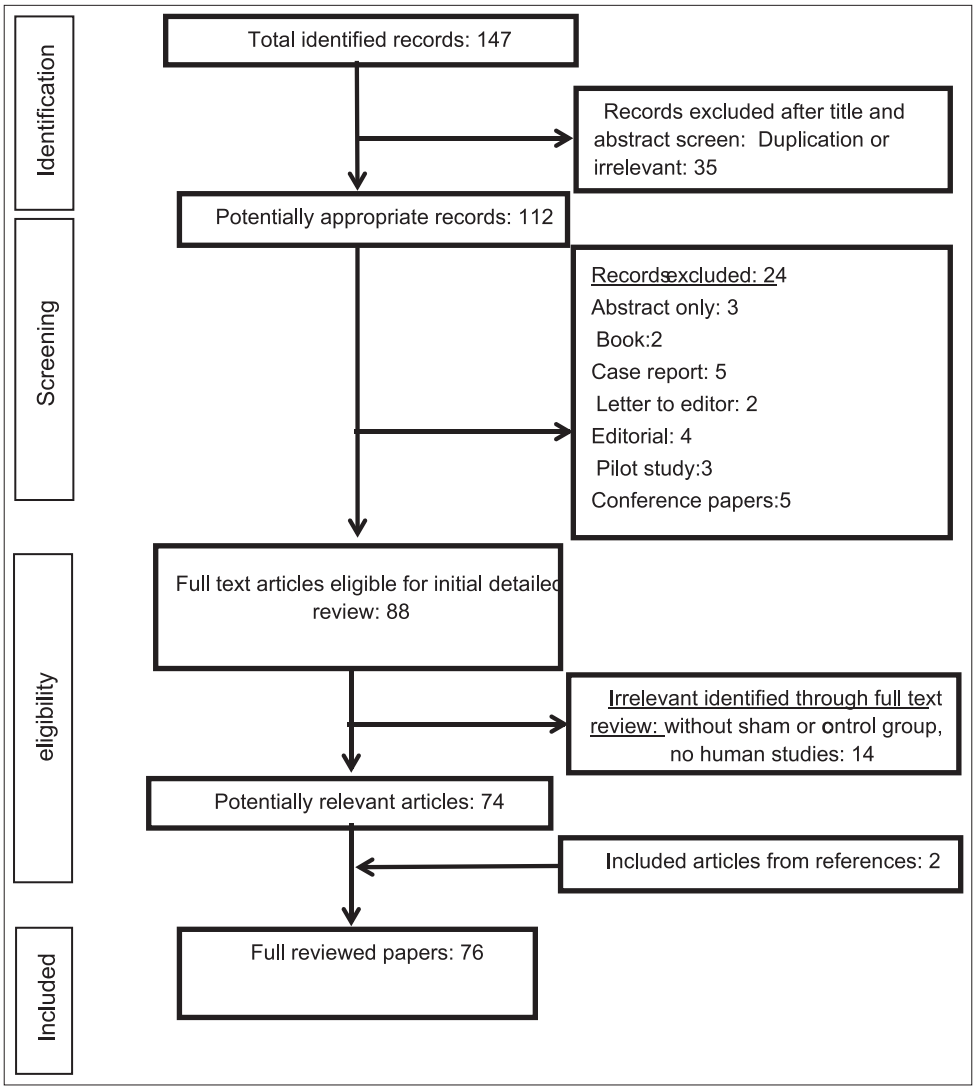

Figure 1: The flowchart of the study design process

between electrophysiological features and metabolic and hemodynamic variables. In depression, excitability of the brain cortex generally decreases.[20] Therefore, one of the main approaches to treat this disorder is increasing the excitability of brain cortex.[21] Since the approval of rTMS application for the treatment of depression by FDA, the therapeutic efficacies of different protocols of rTMS have been evaluated.[13,22] The main parameters influencing the treatment outcome of rTMS in depression as well as other neuropsychiatric disorders are frequency, magnetic field intensity (defined as the percentage of motor threshold of the subject), site of stimulation, number of pulse per session, total pulses per treatment, and number of sessions per day.[23-25] The LDLPFC and RDLPFC are the most common sites for the rTMS applications. The low frequencies rTMS (≤5 Hz) are usually applied on RDLPFC, whereas high frequencies rTMS are used for LDLPFC.[22,26-29] Neuroimaging and neurophysiological studies of the brain have shown that mood is regulated by a network consisting of different brain regions including prefrontal, cingulate, parietal, and temporal cortical regions. This network is functionally connected to different regions of the striatum, thalamus, and hypothalamus. Therefore, we can expect that any anomaly or lesion in any part of this network would result in mood disturbances. Furthermore, in the depressed patient's alterations in cerebral blood flow and metabolism in different regions of this network mainly the medial frontal, dorsolateral, and orbitofrontal regions. One of the main regions inside this network is DLPFC which is responsible for depression and highly connected with other crucial nodes in the network such as other prefrontal and anterior cingulate regions.[22,27-30] Therefore, the first line of rTMS studies in depression has focused on DLPFC as a site of stimulation.[15,22,23,26,27,31-34]

The previous comprehensive meta-analysis studies on the randomized clinical trials reported a moderate to strong order of mean weighted effect size of rTMS compared to sham stimulation in depression treatment that ranged 0.65-0.89.[35-37] The findings of previous meta-analyses showed that rTMS is associated with clinically relevant antidepressant effects.[31] An interesting feature of rTMS for depression treatment is high level of safety and tolerability profile or rTMS. The previous studies have demonstrated the therapeutic efficacy

of rTMS in depression patients both for drug resistant and nondrug resistant patients.[31,34,38]

A typical rTMS treatment protocol for depression treatment consists of a 20-40 min session with total of 3000-6000 pulses at 10 Hz, 5 or 6 days a week for 4-8 consecutive weeks. In rTMS studies, left and right DLPFC are the most used sites of stimulation with corresponding 10 and 1 Hz frequency of stimulation. The neurophysiological effects of low-frequency rTMS are significantly different from the high-frequency stimulation. Low-frequency rTMS modulates frontal alpha power asymmetry, whereas high-frequency protocols influence more broader regions and wider electrophysiological characteristics of the brain.

rTMS for hallucinations

The unique features of rTMS targeting specific regions of the brain, stimulating deep-seated brain areas, and inducing modulation in neural network have convinced the researchers to investigate the efficacy of rTMS for treatment or inhibition of different types of hallucinations.[39,40]

Hoffman *et al.* were the first group reported the possible therapeutic efficacy of the rTMS over the left temporoparietal cortex in auditory-verbal hallucinations in schizophrenic patients.[41,42] They stimulated the left temporoparietal cortex that intercepts with the Wernicke's area, which is the speech perception area. Neuroimaging and event-related potential studies in patients with hallucinations have demonstrated that the Wernicke's area is hyperactive.[43,44] Considering the hyperexcitability of the auditory cortex in one hand, and the inhibiting effect of low-frequency rTMS on the other hand, has formed the main principal idea of stimulating 1 Hz rTMS over left temporoparietal cortex for the treatment of auditory-verbal hallucinations.

The meta-analysis studies conducted so far on the previously published studies have reported the weighted effect sizes in the order of moderate to high ranging 0.44-0.76.[45,46] In addition, the improvements persisted for about 10-14 weeks. However, it should be noted that the improvements were specific for hallucinations but did not improve other symptoms of the schizophrenia. Most of the studies so far conducted for the treatment of hallucinations have used relatively the same treatment protocol. The site of stimulation was left temporoparietal area, daily 15-20 min session with frequency of 1 HZ for 5-10 days, intensity ranging 80-100% of motor threshold. However, there were some studies with different protocols and over the different sites of stimulation including daily two sessions[47,48] and stimulating left auditory cortex.[49]

There are also some studies that have failed to significantly improve the auditory-verbal hallucinations or with low improvements.[47,49-51] One of the main reason for these controversial findings can be attributed to the different pathologies of the disorders which need disease-specific protocol. In addition, in some of these studies, the stimulation site was not the left temporoparietal cortex: Some studies targeted the left auditory cortex,[49] some studies stimulated right temporal region[52] and the other studies used bilateral paradigm for stimulation.[51]

Although some of the recent studies have reported negative findings, combining them with the studies with positive outcomes resulted in a relatively moderate weighted size effect (about 0.44) indicating promising outcomes which is still statistically significant.[46] However, the effect was no longer significant at 1 month follow-up.

rTMS in other psychiatric disorders

Different protocols of rTMS have been investigated for treatment of other neuropsychiatric disorders and conditions including substance abuse, schizophrenia, OCD, and PTSD, although studies on these conditions are in early stages, the general census is therapeutic efficacy of rTMS on these conditions. Clinical application of rTMS has not been approved by FDA for any of these disorders; however, clinical applications as research tool are encouraged.

Schizophrenia

Different protocols of rTMS have been investigated for improving negative symptoms in schizophrenia.[53-56] The findings were relatively promising; however, the findings were controversial. A meta-analysis review of nine clinical trials (n = 213 patients) showed that active rTMS could significantly improve the negative symptoms of schizophrenia compared with the sham rTMS.[57] However, the average weighted effect size was in the order of small-to-medium range (d = 0.43).[57] In a more recent, meta-analysis performed by Freitas *et al.* on the efficacy of active rTMS versus control or placebo rTMS on negative and positive symptoms of schizophrenia they concluded moderate and significant effect sizes of active rTMS versus placebo stimulation.[58] They reported significant and moderate effects of rTMS on negative and positive symptoms (d = 0.54 and d = 0.58, respectively). However, the effect size for the placebo or control rTMS was small and non-significant for both negative (0.27, P = 0.417) and for positive symptoms (0.17, P = 0.129). The findings of this study along with other randomized clinical trial have claimed that rTMS may be more effective in treatment of positive symptoms of schizophrenia rather than negative symptoms.[59,60] One of the findings of the previous studies in this disease is that rTMS protocols with longer duration of treatment (≥3 weeks) showed a larger mean effect size compared with the shorter treatment period. The common site of stimulation in schizophrenia was left DLPFC; however, the right DLPFC may have therapeutic value as the site of

stimulation as several neuroimaging studies have shown the involvement of this site in the progression of the disease.[61,62]

OCD

Several studies have been conducted on the efficacy of rTMS in OCD.[63-68] In a systematic review performed by Jaafari *et al*., they reviewed 12 studies including open and randomized, sham-controlled trials.[63] They reported that two brain regions may be good candidate as site of stimulation in rTMS treatment for OCD including supplementary motor area and the orbitofrontal cortex.[63] In a more recently published study with 3-month follow-up, conducted on 22 OCD patients, the findings showed that active rTMS was significantly better in reducing the OCD symptoms compared with the placebo group (35% vs. 6.2% reduction).[64] Berlim *et al.* in a meta-analysis (10 studies, $n = 282$) on the efficacy of active rTMS versus placebo or control stimulation reported a moderate and significant weighted size effect of rTMS versus placebo ($d = 0.59$) for improvement of OCD symptoms.[69] The response rates for active and placebo rTMS were, respectively, 35% and 13% (odds ratio = 3.4, $P = 0.002$).[69] There were also some studies on the efficacy of rTMS in OCD treatment with no significant improvement in the symptoms. Sarkhel *et al.* reported that high-frequency rTMS as an adjunctive treatment over right prefrontal cortex was not effective in OCD, while it significantly improved the comorbid secondary depression.[70] Reviewing the findings of randomized clinical trials as well as the previous conducted meta analyses, the main findings on the efficacies of rTMS for OCD treatment are as follow: Low frequencies rTMS are more efficient than high frequencies. The sites of stimulation including orbitofrontal cortex and the supplementary motor area are more likely to respond to the treatment compared with the DLPFC or temporal or temporoparietal cortices.[66,69,71-74]

PTSD

Several neuroimaging and electrophysiological studies have demonstrated hyperactivation of the amygdala in PTSD patients.[75,76] Amygdala is a subcortical neural structure involved in the excitatory response to stressors and fearful situations through encoding and consolidation of memories for traumatic phenomena.[77-79] The site of stimulation for treatment of PTSD is DLPFC which is based on the mutual functional connection between this site and amygdala. Neuroimaging and neurocognitive studies on the applications of rTMS in PTSD have proposed that the rTMS possibly exerts its effects through stimulating activity in the prefrontal cortex, which in turn further inhibits the amygdala through a negative feedback circuitry. The deficit in this neural circuit along with the inhibition of sympathetic function is a main reason for specific symptom clusters including hyperarousal present in PTSD patients.[80] In PTSD patients with minor head trauma, the inhibitory function of the cortical neurons is reduced. Therefore, the inhibitory effects of low frequency rTMS on cortical neurons are probably the underpinning mechanism of its therapeutic effect.

Few studies have investigated the efficacy of rTMS in PTSD. Watts *et al.* reported that 10 sessions of 1 Hz rTMS over the right DLPFC significantly reduced (30% reduction) the PTSD symptoms compared with the sham group.[81] Conducting more studies with large sample size is necessary to reach a conclusive finding in this regard. The previous studies have indicated the effectiveness of TMS for PTSD. In addition, the main region of stimulation has been reported the DLPFC and the right DLPFC showed more treatment response than the left counterpart. There is relatively significant evidence indicating effectiveness of rTMS for PTSD. Reductions in the severity of PTSD symptoms were observed in a case study of 1Hz rTMS applied to the right prefrontal cortex.[82] A single session of bilateral motor cortex stimulation reduced the avoidance symptoms and increased treatment response within the first 24 h post-treatment.[83] In a randomized controlled trial, 10 sessions of either 1 Hz rTMS or 10 Hz rTMS over the right prefrontal cortex were compared with a sham rTMS group, and the findings showed the active rTMS significantly reduced the severity of symptoms. A significant reduction of anxiety was also detected in the 10 Hz rTMS group. Interestingly, these effects lasted for about 2 weeks poststimulation. The overall findings of the rTMS studies on PTSD show the effectiveness of either low or high frequency rTMS in PTSD patients.

In a meta-analysis conducted by Trevizol *et al.* on the efficacy of rTMS for PTSD treatment evaluated five randomized clinical trials (total sample size = 118) in an active-sham rTMS assessment. They reported that active rTMS was significantly more efficient than the sham rTMS for PTSD symptoms (Hedges' $g = 0.74$; 95% confidence interval = 0.06-1.42). Although the heterogeneity was significant in their analysis ($I^2 = 71.4\%$ and $P = 0.01$ for the χ^2 test), the exclusion of the study with significant heterogeneity did not significantly change the effect size significant impact on the results.[84] They concluded that active rTMS was more effective than the sham stimulation in reducing the PTSD symptoms.

The current evidence on the efficacy of rTMS for treatment of PTSD is relatively moderate. However, the heterogeneities in methods and studied parameters as well as the stimulation parameters associated with these studies are the main barrier for conclusive statement on the efficacy of the rTMS in PTSD.

CONCLUSION

Repeated sessions of low frequency (≤5 Hz) rTMS induce long lasting neural inhibition or depotentiation, whereas high frequency (>5 Hz) induces long lasting neural excitability or potentiation. Depending on the neural alteration induced by a

disorder, low or high frequency rTMS is used for treatment. rTMS is approved as acute treatment for major depression. Among different protocols, 10 Hz rTMS over the left DLPFC can improve depression. The other diseases with promising outcomes are different hallucinations, OCD, tinnitus, substance abuse, mania, epilepsy, and migraine. rTMS seems to be an alternative or adjunctive therapeutic modality in different psychiatric disorders. However, because of small sample size and the heterogeneities existed among the performed studies on each of these disorders, no conclusive outcome on the efficacy of this technique can be reached. To reach efficient clinical application for each disorder, further randomized clinical trials as well as preclinical studies are needed.

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