Dis Mol Med 2013;1: 77-86

disease & molecular medicine

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Review Article

A Review of Repetitive Transcranial Magnetic Stimulation Use in Psychiatry

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Received: November 24, 2013
Accepted: December 10, 2013

Dis Mol Med 2013;1: 77-86
DOI:10.5455/dmm.20131210021723

Key words: *rTMS,review,meta-analysis,efficacy,psychiatry*

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique first introduced by Barker et al. in 1985. The principle of rTMS is based on a cortical neuronal transmembrane potential stimulated by a pulsative magnetic field. This magnetic field is induced by a direct electrical current sent through a circular coil. rTMS is an effective and widely used therapeutic stimulation method for psychiatric disorders, primarily for unipolar depression. Cost-effectiveness, minor side effects and well-tolerated profile of rTMS with no need to hospitalization for administation are the prominent features of this method. Beside the information for depression, rTMS has been reported to have some remarkable impacts in alleviating symptoms of anxiety disorders. Although data regarding efficacy of rTMS in anxiety disorders is conflicting, there are positive outcomes about generalized anxiety disorder, post-traumatic stress disorder and panic disorder whereas results of rTMS treatment in obsessive-compulsive disorder are generally not favorable. Since low frequency stimulation techniques have been found to be effective in treatment of auditory hallucinations, methodological similarity in concerned studies could be accepted as a supportive aspect of efficacy. Additionally, high frequency stimulation techniques applied to prefrontal area have a potential to impact negative symptoms of schizophrenia. With improving novel techniques of this stimulation method, rTMS is being used increasingly in psychiatric disorders. However, some issues concerning rTMS treatment such as maintenance or prophilactic therapy procedures, duration of effect are remain unclear. Hence, we conclude that multicenter sham controlled studies including similar designs, sociodemographic and clinical variables, methodological protocols with larger sample sizes and studies guieded by imaging methods are warranted to determinate efficacy and side effects of rTMS use in psychiatric disorders.

Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation technique first introduced by Barker et al. in 1985. The principle of rTMS is based on a cortical neuronal transmembrane potential stimulated by a pulsative magnetic field. This magnetic field is induced by a direct electrical current sent through a circular coil(1,2). This stimulation can be applied as a single pulse or repetitive mode and be effective in cortical and subcortical areas up to a depth of 1.5-3 cm beneath the scalp. Repetitive pulse protocols are more preferable and widely used owing to its long lasting effects caused by LTD (Long-term depression) and LTP(Long-term potentiation) in neuronal synaptic areas. Beside the fact that TMS has been used as a diagnostic tool in several neuropsychiatric disorders

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since its first description, rTMS took an important place between somatic treatment methods in psyhiatric disorders in last two decades, particularly in refractory depression treatment, as a candidate of alternative to electroconvulsive therapy (ECT). Although the efficacy of rTMS has been proved by several meta-analyses and reviews, a remarkable heterogenity in treatment outcomes exists (3). We think that the reason of this heterogenity is the use of different treatment protocols in these studies.

There are some theories about the mechanism of rTMS. Neuromodulation, neuroplasticity, neuronal excitability, modulation in secretion of endogenous dopamine and some neurotrophic factors like BDNF (Brain-derivated neurotrophic factor) and alteration of serotonergic and dopaminergic receptor levels are the main ones to explain the mechanism of this treatment (4-7). Positive impact of first rTMS applications yielded improvements in magnetic stimulation technology. "Theta burst rTMS" and "Deep TMS" are novel forms of rTMS (8). Theta-burst rTMS has ability to induce strong and long lasting cortical excitability with lower stimulation intensity and shorter stimulation time compared to conventional rTMS protocols (9). Deep TMS enable neuronal stimulation up to a depth of 6 cm including subcortical areas using H coil. There are some studies demonstrated the efficacy and safety of deep TMS in depression and cognitive functions (10,11).

Application of rTMS

In rTMS application circular coil is usually placed upon scalp with 450 degree angled to midsagittal line. Figure-of-eight shaped or butterfly coil is the most used coil in this procedure. Beside butterfly coil, some round coils can be used but their efficacy is low. The most studied psychiatric disorder about efficacy of rTMS is major depression while dorsolateral prefrontal cortex (dLPFC) was chosen as application area in most of previous studies. "5 cm method" is the most preferred procedure for the coil positioning to dLPFC. In this method single pulse stimulation is delivered the precentral cortex to determinate motor cortical site and motor threshold by observing consecutive 5 controlateral hand muscle contraction (particularly abductor pollicis brevis and interosseous muscles) during stimulation. Afterwards, coil is moved forward 5 cm anterior to hand motor hotspot in parallel line to parasagittal axis. Because the reliability of this method is obscure, and it is subjective, determination of motor threshold should be done by performing EMG to get objective and reliable outcomes (13,14). Motor threshold is described as lowest intensity of stimulation to produce 50 μV amplitude MEP (motor evoked potential) in EMG practice. Neuronavigation procedures of rTMS have been studied in recent trials. Despite the fact that neuronavigation systems appeared to be superior to conventional method of rTMS applications in some studies (24), therapeutic value of these systems remain unclear(14).

Variable Parameters in Practice

Repetitive Transcranial Magnetic Stimulation procedure includes some parameters particular in response such as frequency, intensity and number of pulses. The treatment response found to be superior in recent trials used protocols including more number of sessions higher intensity and frequency of stimulation, compared to earlier studies in which protocols were with less number of sessions, lower frequency and intensity of stimulation. Based on this data, it is accepted that protocols of rTMS with longer treatment periods and with higher intensity and frequency of stimulation are more effective in terms of treatment response. There are two main types of stimulation in rTMS clinical practice: low frequency (<1 Hz) and high frequency(>1 Hz) stimulation. These two types of stimulation have opposite effects that high frequency stimulation increase neuronal excitability while low frequency stimulation induce inhibitory effect in neuronal transmembrane potential. It is supposed that right and left hemispheres have contrasting roles in mood regulation and depression. Because the reduced left prefrontal activity seem to be significant in depression, many of studies have been designed with high frequency protocols. Beside to this information, in literature, there are several studies used low frequency protocols based on the theory that stimulation at low frequency to right prefrontal cortex can reduce excessive activation in this region by its inhibitory effect.

Side Effects of rTMS in Clinical Practice

Repetitive Transcranial Magnetic Stimulation is generally regarded as a safe stimulation method hence it is approved technique and used widely in several neuropsychiatric disorders. Because it is a stimulation method, some constraints bring along in clinical practice. First of all, owing to possibility of induced epileptic

seizures particularly in high frequencies, it can be dangerous in epileptic patients or in clinical situations associated with developing seizure (increased intracerebral pressure, using drugs lowering seizure threshold). This method is not offered to patients with epilepsy or with increased intracerebral pressure especially with high frequency protocols. Additionally protocols with higher intensity more than 130 MT, 25 Hz frequency are associated with increased risk of seizure. Therefore, safety of protocols which include parameters exceeding the limits that are given (130 MT,25 Hz) is not studied well and remain unclear(14). Although it was reported that rTMS applications are with increased risk of epileptic seizure, it was found that risk of seizure induced by rTMS is as low as %1.4 percent in epileptic patients(16). There are limited number of reports about seizures induced by low or high frequency applications in literature (15). It was revealed that most of cases in which seen seizures induced by rTMS have predisposed features to develop seizure and that seizures were transient with short duration while EEG abnormalities accompanied by seizures were overed following a couple of days(13). However, contrarily to this data, there are some reports about the use of low frequency rTMS based on its inhibitory effect in epilepsy treatment(12). Although rTMS is often regarded as safe, there are some reported side effects of this application. Seizures induced by stimulation are the most severe acute side effect of this method. Headache and local discomfort, transient changes in auditory threshold, vasodepressor syncope, facial twitching, tearfulness, local erythema and dizziness are the other side effects seen more often in high frequency applications(17). The side effects associated with rTMS are generally transient and occur in %15-20 percent of patients. Headache is the most often side effect after this treatment with %10 percent of occurence while it can be relieved by a simple analgesic medication(16,17). Both operator and subject should wear earplug with a rating of 30 dB of noise reduction during treatment for their comfort and hearing protection. The other dimension of side effects seen in rTMS, cognitive side effects such as dizziness, concentration difficulties and memory problems, were reported to be transient and mild in a meta-analysis(19). Contrary to this, posttreatment cognitive improvement were reported in 12 of 39 sham controlled studies were included in a recent review of rTMS safety in clinical depression(20). Janicak et al. reported no cognitive effect of TMS in subjects with major depression in a randomized sham controlled trial over 10.000 cumulative treatment sessions administered in(21). Another concerning side effect of this stimulation method is induced manic shift in depressive subjects. Although there are some single case reports about treatment-emerged mania, overall rate appears to be as low as percent of %0.84 regarding to depression studies(14). Similarly there are some cases reported about treatment emerged psychotic symptoms or suicidal thoughts in literature but whether these occur due to the natural course of disease or interventions during treatment is remain unknown(14). Treatment emerged suicidal ideation or psychotic symptoms have never been in healthy subjects. Neuroendocrinological impacts of rTMS is another aspect of after-effects in treatment. rTMS was found to be associated with measurable changes in serum levels of cortisol, prolactin, BDNF and TSH(14,22). Effects of rTMS on immune system is remain obscure at this time. There are few papers adressing this issue in literature. Left and right hemispheres play contrasting regulatory role on immune system. Left hemisphere stimulation can increase circulating lymphocytes numbers whereas right hemisphere stimulation can decrease them. An increase of CD8-T lymphocytes was determinated after left-sided single pulse stimulation whereas decrease after right sided single pulse stimulation in a study as a support to this information(13).

Important Considerations During Application

Metallic objects in the head can be moved or heated by magnetic field. Therefore persons who have implanted or non-removable metallic objects in the head (e.g. cochlear implants, implanted brain stimulators, ocular implants, aneurysm clips or stents),except the mouth, should be excluded. Individuals with cardiac pacemakers and implanted medication pumps also should not get rTMS therapy. Subjects diagnosed with epilepsy, serious cardiac or metabolic diseases, intracranial problems (e.g. increased intracranial pressure, central nervous system tumors, cerebrovascular disease, head trauma), alcoholism, those who use medications lowering seizure threshold or are sleep deprivated should be evaluated and informed carefully about the risk/benefit ratio of rTMS therapy. Although the safety of rTMS in pregnancy is not well known yet, there are some reports presented positive outcomes and supporting the data that includes this method can be a good alterna-

tive for pregnant women diagnosed with major depression (23).

Featured Factors in Application

Primarily, chosen parameters of application are very important in treatment response. The parameters of rTMS consist of intensity, frequency, train duration, intertrain interval, number of pulses per session and total number of sessions. In a recent review, it was emphasized that rTMS applications administered with parameters included more than % 100 MT,1000 pulses per session and 10 of total session are more efficient in treatment of depression(25). There are different types of application in clinical practice of rTMS such as HF session applied left dLPFC following LF right dLPFC session or bilateral HF dLPFC session apart from HF dLPFC application. There are several factors, including menstrual cycle, age,alcohol/susbtance use comorbidity, sleep deprivation,current medications, anxiety level, that can be efficient in neuronal activation of application area. Additionally, position of coil, stimulation area, coil-cortex distance which can be important especially in old patients due to presence of cortical atrophy, clinical severity are the other main factors that can influence treatment outcome(14,26). History of response to rTMS has been reported to be a positive predictor for the following rTMS applications(25,27). There are some imaging trials emphasized that metabolic findings including decreased activity and hypoperfusion in left dLPFC and temporal region can play a role in response to rTMS treatment(25,28,29). Improvement of decreased metabolic activity in cerebellar, temporal, anterior cingulate and occipital regions after two weeks of 20 Hz rTMS application is another reported metabolic finding showed by imaging trials(25). Additionally, in some recent studies it has been reported that resting motor threshold(RMT) changed by rTMS is related to clinical response(33,34).

rTMS and Depression

The most well known and accepted clinical indication of rTMS application is depression. Moreover, it is the clinical disorder which has the most number of rTMS studies in literature. In 2008, FDA has approved rTMS for depression in cases of inadequate response to one antidepressant medication adminisitered with adequate dosage and period. It is obvious that majority of studies target left dLPFC as stimulation area in treatment of depression. As depression and prefrontal cortex is considered to be relevant , ventromedial prefrontal cortex (vmPFC) and dLPFC play significant role in pathophysiology of depression. dLPFC is responsible for executive functions, sensory cortical inputs and voluntary emotion regulation, while vmPFC is rather associated with affective components including involuntary emotion regulation, visceral autonomic activity and reward mechanism by its intensive reciprocal connections with amygdala and hypothalamus(35,36). As it is well known that executive functions impair considerably in depression. Supporting to this data, in some studies, hypoactivity of dLPFC whereas hyperactivity of vmPFC was reported in depression(37,38). In addition to dLPFC, reductions in hippocampal volume and anterior cingulate cortex (ACC) activity are other reported changes thought to be yielding decrease of inhibitory effect on amygdala, hence stimulation at HPA axis by hyperactivity of amygdala and concomitant hypercortisolemia emerged neurotoxicity resulting cell loss in prefrontal region and hippocampus , onset of depressive symptoms including apathy, psychomotor retardation, impairment in executive functions and emotion regulation(39-41). The theory including most used and approved stimulation method in depression, HF stimulus to left dLPFC, emerges cortical neuronal activity in application area, thus improves depressive symptoms and comorbid executive functions, is one of acceptable theories regarding mechanism of rTMS in depression. LF stimulation to right dLPFC is the second most used method in depression subsequently. This method is based on the principle of decreasing the overactivity in right hemisphere by inhibitory effect to ameliorate left hemisphere activity reduced by right hemisphere(3,30,42,43). It was reported that LF method is more favorable regarding its better side effect profile, that it is well tolerated and has similar efficacy compared to HF method(8,30,44). Bilateral stimulation methods were also found to be effective in depression(8,30). Although studies evaluated the efficacy of these alternate methods in rTMS treatment are promising, a recent review point out the need of further trials with larger sample size(30). Efficacy of rTMS that was approved in depression is limited by medication free patient group. However, particularly recent studies showed that rTMS augmentation is effective as much as monotherapy in treatment of depression. A meta-analysis reported that efficacy of rTMS monotherapy is superior to add-

on treatment in depressive subjects(17). Psychomotor retardation, high level of sleep disturbances, low level of agitation, young age, existing no psychotic features, positive outcome of rTMS/ECT treatment before, low score of treatment resistance were reported to be positive predictors of rTMS treatment response whereas feelings of guilt, high level of depressed mood were negative predictors(31). Clinical trials comparing the efficacy of rTMS and ECT have yielded that rTMS is significantly efficient stimulation method but inferior to ECT for treating major depression and depression with psychotic features(17). Therefore, rTMS can be considered as an alternative option prior to ECT in management of treatment resistant depression(32). Along with there is insufficient data considering rTMS application as a conservative or maintenance therapy(45), mean duration of antidepressant efficacy was reported approximately 5 months(46,47).

rTMS and Bipolar Disorder

Although together with unipolar depression rTMS particularly including novel methods like H-coil application has been reported efficient in bipolar depression, larger controlled studies are needed to optimize stimulation parameters of rTMS use in bipolar disorder(45,48,49,52). To the best of our knowledge, direct comparison of efficacy of rTMS in unipolar and bipolar depression has not been reported yet. Therefore efficacy of rTMS in bipolar depression needs to be clarified and confirmed by future studies. There are only a few reports about efficacy of rTMS in bipolar mania(50-52,54). Along with worsening of manic symptoms by HF stimulation applied to left PFC has been reported(50), most of manic cases with positive outcome after rTMS treatment were applied HF stimulation to right PFC. rTMS induced manic shift is a considerable complication similar to other antidepressant therapies, and particularly in bipolar depression management. Total of 13 cases with manic shift after rTMS therapy were reported in a review published in 2008, whereas manic shift risk was estimated approximately percent of %0.89 and %0.73 in patient and sham group respectively, concluding manic shift risk is not statically significant but with a mild raising after rTMS treatment of bipolar depression(55).

rTMS and Auditory Verbal Hallucinations(AVH)

Another clinical condition that rTMS treatment can be used in is auditory verbal hallucinations(AVH). There are already remarkable reports regarding low frequency rTMS applied over temporoparietal (TP) region as a therapeutic tool in treatment of AVH by inhibitory effect. In clinical trials confirmed efficacy of rTMS in auditory hallucinations, similar protocols including 1 Hz frequency, TP region, %80-100 of MT intensity, 4 to 10 days of course, 900-1600 pulse per session were performed(17,60). However, trials with larger sample sizes have demonstrated no superiority of rTMS as compared to sham. A meta-analysis published in 2010, including 7 randomized sham-controlled studies of rTMS for AVH in mostly treatment resistant patients , 6 of those with LF (1 Hz) stimulation applied over left TP region whereas 1 of those with LF to right TP region, concluded rTMS as a treatment method for AVH with moderate efficacy(17). A recent meta-analysis consisting of 17 randomized-controlled studies of rTMS for AVH revealed that number of dropouts in real rTMS group was not higher than sham group in addition to finding of duration of effect was not more than one month. In 2011, Slotema et al. performed a clinical trial considering efficacy of rTMS in AVH and whether fMRI guided rTMS method could enhance clinical outcome with 62 treatment resistant AVH patients and it was reported that neither LF-rTMS to left TP region nor to maximal hallucinatory activation area detected by individual fMRI scans was not more efficient than sham treatment(58). Even though it was suggested that "priming" method that is characterized by pretreatment brief (5 minutes) HF (6 Hz) rTMS phase prior to LF-rTMS could enhance the response to rTMS in treatment of AVH, conflicting data also present in available literature. Blumberger et al. reported that neither priming nor LF left sided rTMS Heschl's gyrus within TP region is effective in treatment of refractory AVH in schizophrenia(59). Nevertheless rTMS use has been proposed as a good alternative option for particularly refractory AVH, evidence is still lacking in terms of protocol of application, duration of treatment, prophilactic and maintenance treatment modalities. HF rTMS to left dLPFC has been investigated in positive symptoms (apart from AVH) of schizophrenia based on theory that hypofrontality could play a role in positive symptoms by disinhibition of temporal cortex, but results found to be conflicting. There are reported positive outcomes whereas neutral and even negative outcomes of rTMS with worsening after applied for positive symptoms of schizophrenia in literature (60).

rTMS and Negative Symptoms of Schizophrenia

Negative symptoms of schizophrenia are commonly associated with hypofrontality(60). There are some open label and randomized controlled clinical trials for treatment of negative symptoms, based on the theory that HF-rTMS could induce cortical excitability and hence improve hypofrontality, yielded positive and some negative outcomes(60). In these studies variability in design and protocols is prominent and could be responsible for obscure outcome whereas possible overlap of depressive smyptoms –on which rTMS has an apparent efficacy potential- and deficit symptoms also should be considered. A recent randomized double blind sham controlled study enrolled 25 schizophrenia patients with 22 healthy controls and aimed to compare pre and post-treatment changes with rTMS method (including parameters of 10 Hz, %110 MT and total of 15 sessions) in working memory (a core cognitive function that can be impaired in schizophrenia) evaluated by fMRI findings showed no significant differences between two groups(61). However, in another recent sham controlled trial showed a favorable impact of HF rTMS application on cognitive functions in 19 patients of schizophrenia and it is well tolerated stimulation method(62). A meta-analysis including 9 randomised controlled studies, published in 2010, reported that rTMS was efficient in impaired cognitive functions of schizophrenia whereas efficacy was correlated with treatment course(63). Nevertheless, rTMS could have some remarkable positive effects on cognitive functions with increased excitability of prefrontal area in treatment of negative symptoms of schizophrenia, futher sham controlled studies with larger sample sizes are warranted in order to clarify optimal parameters of this stimulation method in negative symptoms of schizophrenia(60,63).

rTMS and Anxiety Disorders

Although anxiety disorders are common and important mental illness as depression, efficacy of rTMS treatment on anxiety disorders is less well established(64,67). On the other hand, since the most of protocols used commonly in rTMS applications are to stimulate the cortical area whereas pathophysiology of anxiety disorders are thought to be included predominantly subcortical areas indicate the need of further studies even with imaging guides(64). An fMRI-guided study conducted by Bystritsky et al. enrolled 10 samples reported that rTMS was effective in treatment of generalized anxiety disorder (GAD)(65). As there are some reports regarding right-sided high frequency rTMS as an effective method in treatment of post traumatic stres disorder (PTSD), right sided low frequency (1 Hz) total of 10 session applied to dLPFC rTMS has been also reported to be efficient in alleviating symptoms of PTSD in a recent sham controlled study(66,67,68). A review mentioned some data considering particularly HF right-sided rTMS applied to prefrontal area efficacy in treatment of panic disorder (PD) and PTSD(72). However, reports about efficacy of rTMS treatment in obsessive compulsive disorder (OCD) are mainly with negative outcomes. In a meta-analysis, published in 2010, total of 3 sham controlled studies conducted in 2001, 2006 and 2007, two of with low frequency (1 Hz) whereas one of with high frequency (10 Hz) , were included to evaluate whether rTMS is effective method in treatment of OCD and results in all confirmed that rTMS was not significantly effective therapeutic tool in OCD. In these studies sample sizes were small (17). Additionally, in a trial, 30 sessions of real rTMS applied to right dLPFC was not superior to sham in refractory OCD(70). Although results considering efficacy of rTMS is OCD are not promising, depressive symptoms that can be seen oftenly comorbid with OCD may improve by rTMS application(71). In an open label trial included 6 PD samples, right sided LF rTMS was found to be effective in relieving depression and panic symptoms, additionally in reducing cortical excitability also(73). Contrary to this data, efficacy of right sided LF rTMS applied to dLPFC in 15 PD patients under SSRI medication has been reported as not significant in a randomized sham controlled study(74).

Other Therapeutic Uses of rTMS

There are some data regarding efficacy of rTMS as a therapeutic tool in treatment of depression in Parkinson's disease or after cerebrovascular accident, cognitive decline causes such as Alzheimer disesase in elderly patients(31). It is important to consider cortical atrophy in elderly population hence higher intensity protocols could be needed for sufficient efficacy. It was reported that, based on its endodopaminergic effect, HF rTMS applied to right dLPFC could be a novel alternative method that should be investigated by future research in ameliorating smyptoms of attention and hypreactivity disorder(ADHD)(75). A review of 2011 reported that HF rTMS have a potential to reduce craving in alcohol, tobacco and cocain dependence but confirming data in

literature is not sufficient yet(76). As it is supported by some studies, rTMS can be also a considerable alternative method for pregnant women owing to limitation of pharmacotherapy(23,79).

Magnetic Seizure Therapy (MST)

Magnetic Seizure Therapy is a method that can be described as inducing a seizure by magnetic stimulation, rather than by electrical current as occurs with ECT under anesthesia. In some recent trials, this novel method has been reported as a promising tool in treatment of depression with better cognitive side effect profile than ECT(77). This method is able to produce a more focal seizure expression than ECT and thus, other brain regions like temporal area may remain intact resulting minimal side effect(78). Although it is early to conclude MST as a treatment option for depression, further studies are supposed to be conducted for optimizing this method in future.

Conclusion

Repetitive Transcranial Magnetic Stimulation is an effective and increasingly being used therapeutic stimulation method for psychiatric disorders, primarily unipolar depression. Cost-effectiveness, benign side effect and well-tolerated profile of rTMS with no need to hospitalize for administation are the prominent features of this method. Most of studies that concluded rTMS as a therapeutic tool for major depression were designed as monotherapy of rTMS whereas recent trials have showed also its significant efficacy as an add-on treatment method for refractory depression. Beside the information for depression, rTMS has been reported to have some remarkable impacts in alleviating symptoms of anxiety disorders. Although data regarding efficacy of rTMS in anxiety disorders is conflicting, there are positive outcomes about GAD, PTSD and PD whereas results of rTMS treatment in OCD are generally not favorable. Since low frequency stimulation techniques have been found to be effective in treatment of auditory hallucinations, methodological similarity in concerned studies could be accepted as a supportive aspect of efficacy. Additionally, high frequency stimulation techniques applied to prefrontal area have a potential to impact negative symptoms of schizophrenia possibly through a reversal of hypofrontality but further studies on larger groups with sham controlled design are needed. With improving novel techniques of this stimulation method, rTMS is being used increasingly in psychiatric disorders. However, some issues concerning rTMS treatment such as maintenance or prophilactic therapy procedures, duration of effect are remain unclear. Hence, we conclude that multicenter sham controlled studies including similar designs, sociodemographic and clinical variables, methodological protocols with larger sample sizes and studies guieded by imaging methods are warranted to determinate efficacy and side effects of rTMS use in psychiatric disorders.

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