Neurosci. Bull. December, 2017, 33(6):747–756
https://doi.org/10.1007/s12264-017-0185-3

www.neurosci.cn
www.springer.com/12264

REVIEW

Updated Review on the Clinical Use of Repetitive Transcranial Magnetic Stimulation in Psychiatric Disorders

Qian Guo[1] · Chunbo Li[1,2,3] · Jijun Wang[1,2,3]

Received: 13 January 2017 / Accepted: 2 August 2017 / Published online: 24 October 2017

Abstract With the ability to modulate cortical activity, repetitive transcranial magnetic stimulation (rTMS) is becoming increasingly important in clinical applications for psychiatric disorders. Previous studies have demonstrated its promising efficacy in depression and schizophrenia, and emerging evidence has also been found in patients with anxiety disorder, obsessive–compulsive disorder, and substance or food craving. However, the overall literature features some conflicting results, varied quality of studies, and a lack of consensus on optimal rTMS parameters. Besides, the efficacy of rTMS in patients with medication-resistant symptoms has drawn most attention from clinicians. Here we review multi-site studies and double-blind randomized controlled trials (RCTs) in single sites, as well as meta-analyses of RCTs in the last three years, in order to update evidence on efficacy and the optimal protocol of rTMS in psychiatric disorders, especially for medication-resistant symptoms.

Keywords Repetitive transcranial magnetic stimulation · Treatment-resistant depression · Schizophrenia · Anxiety disorders · Obsessive compulsive disorder · Substance use disorders

✉ Jijun Wang
jijunwang27@163.com

[1] Shanghai Key Laboratory of Psychotic Disorders (No. 13dz2260500), Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China

[2] Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Ministry of Education, Shanghai Jiao Tong University, Shanghai 200030, China

[3] Brain Science and Technology Research Center, Shanghai Jiao Tong University, Shanghai 200030, China

Introduction to Transcranial Magnetic Stimulation (TMS)

In 1985, Anthony Barker and his colleagues first developed a TMS device and delivered a TMS pulse over the motor cortex [1]. After achieving the delivery of multiple pulses within a short time, known as repetitive TMS (rTMS), researchers managed to modulate cortical excitability that was sustained beyond the stimulation period [2, 3]. Normally, rTMS is delivered in a single session for exploratory experiments or in multiple sessions for clinical treatment. Although modern pharmacological treatments have alleviated the suffering of most psychiatric patients, numerous patients still suffer from drug-resistant symptoms or relapse. Recently, rTMS has been considered a promising novel treatment that has received empirical support in the treatment of psychiatric disorders.

The effects of rTMS depend on the parameters of waveform, frequency, intensity, and duration of stimulation. Due to the lower energy requirements, a biphasic waveform is frequently used in stimulation [4]. Frequency is one of the most important parameters in rTMS protocols that affect the clinical outcome. High-frequency (HF) rTMS usually comprises frequencies $\geq$ 5 Hz, while low-frequency (LF) rTMS includes frequencies $\leq$ 1 Hz. Evidence has suggested that LF rTMS is "inhibitory" while HF rTMS is "excitatory" [5]. Besides single-type stimulation, various new TMS paradigms that combine HF and LF rTMS protocols have been developed. Among these, one popular protocol is "theta burst stimulation (TBS)", in which continuous (cTBS) or intermittent (iTBS) trains are

delivered. Studies in healthy participants have shown that the cTBS protocol is "inhibitory" while the iTBS is "excitatory" [6]. These effects of cTBS or iTBS are due to the mimicking of long-term potentiation or long-term depression of synaptic transmission [7, 8]. Other factors such as the position of the coil, intensity of stimulation, duration of stimulus train, and inter-train interval, as well as the number of stimuli per session, may also affect the outcome of rTMS treatment.

Safety of rTMS

Induction of a seizure is the most important safety concern of rTMS treatment. However, the incidence of seizures with TMS is relatively low and is less evident than that with current antidepressant medications [9]. Overall, the estimated risk of a seizure is < 1 in 30,000 treatment sessions ($< 0.003\%$) or < 1 in 1000 patient exposures with the NeuroStar coil (NeuroStar TMS Therapy User Manual, Neuronetics, Inc., Malvern, PA) and 6 in 5000 patients with the Brainsway coil (User Manual, Brainsway, Jerusalem, Israel) [10]. However, TBS protocols have a potentially higher risk of triggering a seizure than traditional rTMS protocols due to the high-frequency bursts. According to a recent review, one incident of seizure occurred after applying TBS to the primary motor cortex at an intensity of 100% of resting motor threshold (MT) [11]. Therefore, following the original TBS paradigm at 80% of the active MT is highly recommended to lower the risk of seizures [6]. Most rTMS-induced seizures are self-limited, and risk is minimized by adherence to the recommendations of the International Federation for Clinical Neurophysiology [12].

The most common adverse effect reported by patients is scalp pain. The discomfort is transient, and gradually increasing the intensity of rTMS during the first week may prevent it [13]. Vasovagal syncope may also occur at the beginning of a treatment session. Caution should be taken when the patient stands up. The audible clicking sound during rTMS treatment can be reduced by using earplugs [14].

Depression

Depression is a condition with high recurrence and tends to become chronic, $> 10\%$ of chronic patients being resistant to several psychopharmacological interventions [15]. Almost 30% of patients suffering from a major depressive disorder do not respond well to pharmacological, psychotherapeutic, or somatic treatment [16]. Based on the concept of frontal asymmetry in depression, researchers have either administered LF rTMS (inhibitory stimulation) to the right dorsolateral prefrontal cortex (DLPFC), or HF rTMS (excitatory stimulation) to the left DLPFC [17, 18] to relieve depressive symptoms. During the last two decades, rTMS has been among the most promising non-invasive interventions for treatment-resistant depression (TRD) [19]. Here, we mainly update the evidence on the efficacy of rTMS in TRD. Other important issues, such as the durability of the antidepressant effect and the maintenance protocol for rTMS, are also discussed.

Efficacy of rTMS in Depression

According to a recent Clinical TMS Society consensus review, a daily standard protocol of HF TMS to the left prefrontal cortex is considered to have evidence-based effectiveness and safety for treating the acute phase of treatment-resistant depressive patients [13]. However, since LF rTMS is more tolerated and safer, researchers have consistently tried to demonstrate its efficacy in depression and compare it with HF rTMS. In a multicenter randomized controlled trial (RCT) with three arms, the efficacy of active LF rTMS over the right DLPFC was compared with placebo venlafaxine, sham LF rTMS with active venlafaxine, and active rTMS with active venlafaxine in TRD patients [20]. The active stimulation consisted of 360 pulses/session, at 1 Hz and 120% resting MT for at least 2 to 6 weeks (until remission). At the endpoint of this study, similar antidepressant effects were reported across the three groups, with comparable numbers of remitters. These results strongly support the application of LF rTMS as a mono-therapy to treat TRD, and may augment the effect size of LF rTMS in treating depression in future meta-analysis.

With the same purpose of reducing adverse events and improving the efficacy of HF rTMS, a novel low-field EEG-based synchronized TMS device has been developed to treat depression [21]. Recently, Leuchter's group has validated its efficacy in a six-week multicenter study that included 202 participants. Although no difference in efficacy was found between active and sham in the total sample, participants who completed 80% of the scheduled treatments showed a significant decrease in the Hamilton Rating Scale for Depression-17 relative to the sham group [22]. Moreover, participants resistant to medication exhibited more improvement than treatment-naïve participants. This large-sample RCT demonstrates promising efficacy of synchronized TMS with a low-field magnet for treating depression, especially TRD. However, as this study excluded participants who had failed to respond to a monoamine oxidase inhibitor in the current episode, or had a history of failure to respond to rTMS or electroconvulsive

therapy (ECT), the conclusion may be limited to moderate depressive patients.

Two recent meta-analyses have investigated the efficacy of rTMS on TRD [23, 24]. The earlier one included only 7 RCTs, and the latter included 29. Both studies identified significantly better response and remission rates for active rTMS than for sham rTMS. However,the latter meta analysis by Health Quality Ontario [23] reported that the efficacy of rTMS was smaller than his pre-specified clinically important treatment effect, the mean difference of 3.5 points in Hamilton Rating Scale for Depression (HRSD) score. The authors attributed the small effect to the probability that the patients included in this study were more medication-resistant than those in previous studies. In addition, their study showed that a comparison between rTMS and ECT was statistically in favor of ECT. Usually, ECT is thought to be more effective than antidepressants and rTMS and may be the most effective treatment for major depression [25]. A new meta-analysis involving 10 articles and a total of 425 patients also focused on the effects of rTMS and ECT in major depression [26], and found a superior effect for ECT *versus* HF rTMS on response and remission rates. Further subgroup analysis indicated that the superiority of ECT was present in psychotic depression, and HF rTMS was as effective as ECT in non-psychotic depression. In another systematic review with meta-analysis, Berlim's group specifically examined the effect of HF rTMS on the overall response and remission rates in 1371 patients with major depressive diorder (MDD). They concluded that HF rTMS showed significantly higher rates compared to sham rTMS, for both response and remission and was equally effective as an augmentation strategy or as a monotherapy for MDD [27]. Another two meta-analyses focusing on the efficacy of bilateral *versus* unilateral rTMS reported comparable efficacy of the two modalities, with either a general major depressive disorder sample or a TRD sample [28, 29]. The efficacy of rTMS in depression from the most recent studies is summarized in Table 1.

Durability of the Antidepressant Effect of rTMS

Although acute rTMS has shown an antidepressant effect, it remains unclear if, and for how long, this effect persists after acute treatment. A recent meta-analysis that included 16 double-blind, parallel-design RCTs investigated the durability of the antidepressant effect of HF rTMS on the left DLPFC in the absence of active maintenance treatment [30]. In this meta-analysis, most studies had 1–4 weeks of follow-up, and only one study had more than 3 months of follow-up. The results showed that HF rTMS displayed a small antidepressant effect during follow-up, with an even lower efficacy in RCTs with longer (8–16 weeks) compared to shorter (1–4 weeks) follow-up periods. In addition, the after-treatment antidepressant effect was higher in patients who were less severely ill, unipolar, nonpsychotic, treatment-resistant, and on antidepressants.

Efficacy of Maintenance rTMS After the Acute Response

Applying TMS as a maintenance treatment to prevent symptom relapse is of great interest for the clinical management of depression, and is distinct from the re-introduction of TMS with another acute course. It is usually defined as the regularly scheduled use of TMS after acute treatment (e.g., weekly, biweekly, or monthly) over an extended period. Evidence on this issue is mixed and is mostly from open-label studies that included various continuing TMS protocols [31–37]. Recently, a prospective multisite randomized pilot study was conducted to investigate the efficacy of continuing TMS as a maintenance treatment over a 12-month period [38]. In that study, 67 medication-free patients with TRD were randomized to periodic HF TMS over the left DLPFC or only observational regimens after receiving improvement from acute TMS treatment. In the rTMS maintenance group, one rTMS session was delivered monthly. Unfortunately, by the end of the study, there was no statistical difference between the two groups. It is noteworthy that, among the studies prior to this multisite study, positive results were mostly reported in studies applying continuing TMS with a higher maintenance frequency (once or twice per week) or with a tapering phase starting from high frequency. Therefore, well-designed RCTs or multisite studies are needed to investigate continuing TMS with a higher maintenance frequency or with tapering phase sessions.

Schizophrenia

Most patients with schizophrenia suffer intractable symptoms such as auditory hallucinations, negative symptoms, or cognitive impairment, which fail to fully respond to medication. rTMS has been proposed as a useful treatment for patients with schizophrenia, especially those with persistent auditory hallucinations. Evidence suggests that hypoactivity in the DLPFC is correlated with the negative and cognitive symptoms, while positive symptoms, including auditory hallucinations, appear to be associated with hyperactivity in the left temporo-parietal cortex (TPC) [39] (Table 2). Finding an optimal rTMS protocol to target a specific symptomatic dimension in schizophrenia is among the most important issues in clinical studies.

Table 1 Updated evidence on the efficacy of rTMS in depression.

Study	Design	Comparisons and stimulation site	Results or conclusions
Brunelin *et al.* [20]	MS (*n*=170), TRD sample, Treatment time: at least 2–6 weeks	LF rTMS with placebo venlafaxine, Sham rTMS with active venlafaxine, LF rTMS with active venlafaxine Site: right DLPFC	Similar antidepressant effects across 3 groups
Leuchter *et al.* [22]	MS (*n*=202), Treatment time: 6 weeks	Low-field EEG-based synchronized TMS *versus* sham rTMS Site: bilateral prefrontal cortices	Participants who completed 80% of scheduled rTMS improved better than sham rTMS. Patients with TRD benefited more
Liu *et al.* [24]	MA, TRD sample	Active rTMS *versus* sham (7 RCTs)	OR= 5.12 in favor of active rTMS
Health Quality Ontario [23]	SR and MA, TRD sample	Active rTMS *versus* sham (23 RCTs); active rTMS *versus* ECT (6 RCTs)	rTMS *versus* sham: improvement of depression scores: WMD = 2.31, remission and response rates: RR = 2.20 and 1.72; rTMS *versus* ECT in favor of ECT, WMD = 5.97
Ren *et al.* [26]	SR and MA	Active rTMS *versus* ECT (9 RCTs)	ECT superior to HF rTMS in response (RR = 1.41) and remission (RR = 1.38)
Berlim *et al.* [27]	SR and MA	HF rTMS *versus* sham (29 RCTs)	OR = 3.3 for both response and remission rates; HF-rTMS equally effective as augmentation or monotherapy for MDD
Chen *et al.* [28]	SR and MA	Bilateral *versus* unilateral rTMS (7 RCTs)	Non-significant difference in response and remission rates
Zhang *et al.* [29]	SR and MA TRD sample	Bilateral rTMS *versus* unilateral rTMS, and sham rTMS (10 RCTs)	Bilateral rTMS superior to sham rTMS (RR = 3.43) in response rate, but not significantly more effective than unilateral

CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; HF, high frequency; LF. low frequency; MA, meta-analysis; MS, multicenter study; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratios; SR, systematic review; TRD, treatment-resistant depression; WMD, weighted mean difference.

Positive Symptoms

LF rTMS over the TPC has been consistently used to treat drug-resistant auditory hallucinations [40]. A recent systemic review and meta-analysis included 41 RCTs with a total of 1473 participants, to investigate the efficacy of temporoparietal TMS and prefrontal TMS in schizophrenia [41]. Nineteen studies used prefrontal TMS, usually HF TMS over the left prefrontal or left dorsolateral prefrontal cortex. The other 22 studies used temporoparietal TMS, usually over the left temporoparietal region. Comparison between active and sham TMS revealed significant improvement in hallucinations and positive symptom score of the Positive and Negative Syndrome Scale (PANSS) by temporoparietal TMS. On the other hand, there was no evidence that prefrontal TMS or prefrontal TBS is superior to sham TMS in the average hallucination score or positive symptom score. But the authors graded these results as very low-quality evidence, as the quality of trial reporting was frequently suboptimal, with a risk of strong or unascertainable bias. Shortly after this meta-analysis, a double-blind randomized trial focusing on the efficacy of theta burst rTMS over the left TPC in auditory verbal hallucination (AVH) was reported [42]. The dropout rate was remarkably low in this study, 7 of 71 patients failing to complete all 10 TMS sessions. Although both active and sham groups exhibited significant improvement in AVH symptoms and PANSS positive subscales, no difference was found between the two groups. Another meta-analysis was also conducted to focus on the efficacy of rTMS for AVH, and found an effect size of 0.44 for treating AVH and 0.45 for medication-resistant AVH. However, when only 1-Hz rTMS over the left temporoparietal area and sham treatment were compared, the effect size increased to 0.63 in favor of the left temporoparietal TMS. On the other hand, no superior efficacy was found between 1-Hz rTMS over the right temporoparietal area and the sham group [43]. The above updated evidence suggests that LF rTMS over the left temporoparietal region is the most effective modality for treating positive symptoms such as auditory hallucinations, compared with right temporoparietal and prefrontal TMS.

Negative Symptoms

We have identified 3 multicenter studies, all stated to be double-blind RCTs that investigated the efficacy of rTMS for negative symptoms. In the first, the Dlabac de Lange

Table 2 Updated evidence on the efficacy of rTMS in schizophrenia.

Study	Design	Comparisons and simulation site	Results or conclusions
Koops *et al.* [42]	Double-blind RCT (n = 71) for AVH, treatment time: 5 days (2 sessions per day)	TBS *versus* TMS Site: left temporoparietal cortex	Negative results in improvements of AVH, PANSS-positive, and general subscores
Dlabac-de Lange *et al.* [44]	MS (n = 32) for negative symptoms, treatment time: 3 weeks	Bilateral HF rTMS *versus* sham Site: bilateral DLPFC	More improvement in SANS, but not in PANSS-negative symptom scores
Quan *et al.* [45]	MS (n = 117) for sample with prominent negative symptoms, treatment time: 6 weeks	HF rTMS (n = 78) *versus* sham (n = 39) Site: left DLPFC	Significantly improved negative symptoms *versus* sham rTMS
Wobrock *et al.* [46]	MS (n = 175) for sample with predominant negative symptoms, treatment time: 3 weeks	Active rTMS *versus* sham Site: left DLPFC	No superior effect in improving negative symptoms immediately after treatment or 3 month later
Hasan *et al.* [49]	MS (n = 156) for sample with predominant negative symptoms, treatment time: 3 weeks	10-Hz rTMS *versus* sham Site: left DLPFC	No superior effect on cognitive symptoms
Slotema *et al.* [43]	MA, schizophrenia with AVH	Active rTMS *versus* sham (25 RCTs)	Overall mean effect size 0.44; for medication-resistant AVH, mean effect size 0.45; 1-Hz rTMS over left temporoparietal cortex showed mean effect size 0.63
Dougall *et al.* [41]	SR and MA	Temporoparietal, prefrontal or prefrontal TBS *versus* sham or standard treatment (41 RCTs)	Temporoparietal TMS superior to sham in improving hallucinations, PANSS-positive subscores, and global state; prefrontal TBS had superior effect in reducing negative symptoms *versus* sham; other prefrontal TMS only superior as measured by SANS, but not PANSS; authors considered all evidence as very low-quality

AVH, auditory verbal hallucination; DLPFC, dorsolateral prefrontal cortex; HF, high frequency; LF, low frequency; MA, meta-analysis; MS, multicenter study; PANSS, Positive and Negative Syndrome Scale; RCT, randomized controlled trial; SANS, Scale for The Assessment of Negative Symptoms; SR, systematic review; TBS, theta burst stimulation.

group examined the efficacy of bilateral 10-Hz rTMS over the DLPFC for negative symptoms [44]. Thirty-two schizophrenic or schizoaffective patients with moderate-to-severe negative symptoms were treated for 3 weeks. During the 3-month follow-up, significant improvement in negative symptoms was found in the active rTMS group in comparison with the sham group, as measured by the Scale for The Assessment of Negative Symptoms (SANS) but not by the PANSS negative subscales. Later, a larger multicenter study of 117 patients with prominent negative symptoms specifically assessed the effect of HF rTMS over the left DLPFC on the negative symptoms of schizophrenia. This study applied 6 weeks of treatment, much longer than previous studies. The results confirmed the efficacy of HF rTMS over the left DLPFC for treating negative symptoms, and the effect persisted to the end of the 24-week follow-up assessment [45]. Of note, although randomization was applied in this study, the patients included in the active rTMS group doubled those in the sham rTMS group. Therefore, the incomparable sample sizes might have caused bias in statistical analysis and reduced the quality of this evidence. Almost at the same time, another multicenter study reported on the efficacy of left prefrontal HF rTMS in schizophrenia, but among patients with more predominant negative symptoms [46]. Unfortunately, this study yielded no significant difference between the active and sham TMS groups after 3 weeks of treatment or at follow-up day 105. As discussed by the authors, factors such as the greater severity of illness and the magnitude of negative symptoms in this group, the

relatively few stimuli or repetitive sessions, and the high rate of withdrawal may also have partly affected this result. Although 3 weeks is suggested as the minimal duration for rTMS treatment to be effective [47], it seems that this time period is not sufficient for schizophrenia with severe negative symptoms. As in Dougall's systematic review and meta-analysis [41], prefrontal TBS had a superior effect in reducing negative symptoms relative to sham, as in the scores of both SANS and PANSS. Other prefrontal TMS only showed a superior effect as measured by SANS, but not PANSS, while temporoparietal TMS lacked evidence for treating the negative symptoms. The authors regarded above evidence as of very low quality, since skewed data or bias existed in most studies of this meta-analysis. The conclusion was quite different from previous meta-analysis, which reported a moderate effect size of 0.532 in active TMS *versus* sham TMS for treating negative symptoms [48]. A possible reason for such result could be the inclusion of open-studies in this meta-analysis and significant heterogeneity between studies. Therefore, caution should be taken when evaluating the evidence from non-RCTs in clinical practice.

Cognitive Symptoms

A multicenter study of 156 schizophrenia patients recently investigated the cognitive efficacy of rTMS on patients with predominant negative symptoms [49]. The neurocognition of patients was measured in 4 dimensions with the Auditory Verbal Learning, Trail Marker, Wisconsin Card Sorting, and Digital Span Tests. After a 3-week intervention with 10-Hz rTMS over the left DLPFC, no superior effect was found in any of the four cognitive dimensions either immediately after rTMS or in the 12-week extension phase. The authors discussed several possible reasons, such as insufficient intervention period, practice effect, and limited testing domains in cognition. Again, in Dougall's systematic review, the efficacy of rTMS in the cognitive domain in schizophrenia was also examined. As illustrated in their work, no significant improvement in cognitive symptoms of schizophrenia was found with either temporoparietal or prefrontal TMS [41].

Anxiety Disorders

Patients with post-traumatic stress disorder (PTSD), panic disorder, or generalized anxiety disorder (GAD) suffer from brain dysregulation such as neurological over-arousal (e.g. panic and generalized anxiety disorder) or neurological instable-arousal (e.g. PTSD). Although antidepressant drugs or psychotherapy can help relieve their symptoms, some patients still do not fully respond to conventional treatments. Thus, in the following we focus on the updated evidence on rTMS intervention for the treatment of anxiety disorders.

PTSD, Panic Disorder, and GAD

A recent exploratory meta-analysis with 3 RCTs totaling 64 chronic patients assessed the efficacy of TMS over the DLPFC for the treatment of PTSD, and found a significant improvement in anxiety and depressive symptoms after active rTMS compared to sham-TMS [50]. According to this meta-analysis, right-sided DLPFC was more effective than the left-sided treatment, but no clear advantage was shown in high *versus* low frequency. Meanwhile, similar findings were reported in a systematic review of complementary and alternative medicine for PTSD, with grade 'A' evidence (strong scientific evidence) for rTMS [51]. However, this conclusion remains to be confirmed due to the broad patient inclusion criteria, the heterogeneity among studies, and the small sample sizes. Later, another systematic review and meta-analysis confirmed the superior efficacy of dorsolateral prefrontal TMS over sham TMS on PTSD, with 5 RCTs totaling 118 patients [52]. However, the authors stated that the between-study heterogeneity was remarkably high, so clinical trials with uniform intervention protocols might be needed to verify the results. Studies on rTMS treatment for panic disorder and GAD are relatively scarce. Among them, some included small samples and others did not include placebo controls. A recent systematic review in Cochrane Library included two pilot RCTs using 1-Hz rTMS over the right DLPFC to evaluate the efficacy of rTMS as an augmentation treatment for panic disorder. The results showed no superior effect of active TMS as compared to sham [53].

The updated evidence in our review indicates that rTMS is beneficial for patients with PTSD, especially for those with chronic, treatment-resistant PTSD. However, considering the heterogeneity among studies, specific uniform intervention protocols need to be tested in large samples to establish the optimal rTMS modality for PTSD. On the other hand, more well designed RCTs are needed to clarify the efficacy of rTMS in treating PD and GAD.

Obsessive Compulsive Disorder (OCD)

There is evidence suggesting that hyper-excitation within the cortico-striato-thalamo-cortical circuits, including prefrontal and orbitofrontal cortices (OFC), supplementary motor area (SMA), striatum, globus pallidus, and thalamus may be responsible for the symptoms of OCD [54–57]. Therefore LF rTMS has often been applied to the above

regions to test the effect of rTMS on OCD. A recent multicenter study with a relatively small sample of 22 patients demonstrated that 6-week bilateral LF rTMS over the SMA significantly reduced the OCD symptoms and depressive symptoms, compared to sham [58]. Furthermore, this effect was sustained at a six-week follow-up visit. Later, a double blind RCT, with 3 arms and 45 patients, examined the efficacy of 1-Hz dorsolateral prefrontal TMS, 10-Hz dorsolateral prefrontal TMS, and sham TMS [59]. After 10 sessions of treatment, only 1-Hz dorsolateral prefrontal TMS showed significant improvement of OCD and anxiety symptoms. Evidence has also been found for LF TMS over the right OFC in the treatment of OCD. A randomized, double-blind crossover trial with 19 patients revealed that the clinical improvement tended to be larger with active TMS than sham TMS after 1 week of treatment [60]. At the same time, with PET scanning, the authors reported lower metabolism in the bilateral orbitofrontal lobes in active TMS *versus* sham TMS, supporting the inhibitory effect of rTMS on the OFC. Besides the LF rTMS protocol, we also identified one protocol using αEEG-guided TMS over the bilateral DLPFC to be significantly helpful in reducing OCD symptoms and the related anxiety, compared to the control group [61]. The individualized αEEG-guided TMS, though yielding different outcomes from the effect of HF TMS reported by Elbeh's group [59], conflicts with the theory of inhibiting hyper-excited circuits. Therefore the efficacy and mechanism of αEEG-guided TMS for treating OCD might be examined with larger samples in future.

Substance Use Disorders, Addiction, and Craving

Current pharmacological and behavioral therapies have limited efficacy in reducing craving and the high relapse rate of substance use disorders. Supported by evidence that the DLPFC plays an important role in top-down inhibitory and reward circuits, the use of rTMS over the DLPFC could shed light on nonpharmacological methods of treating substance use disorders.

Recently, Dinur-Klein's group investigated the preclinical efficacy across three TMS protocols, 10-Hz rTMS, 1-Hz rTMS, and sham stimulation, over the prefrontal and insular cortices in a large sample of 115 treatment-seeking smokers. The results showed that HF rTMS significantly reduced cigarette consumption and nicotine dependence compared to LF rTMS (1 Hz) and sham rTMS, achieving abstinence rates of 44% by the end of treatment and 33% at 6-month follow-up [62]. On the other hand, though it suggested that food craving is also associated with DLPFC activity, a recent double-blind RCT delivering 10 rTMS sessions to 47 female patients with bulimia nervosa failed to demonstrate any greater benefit from active than sham rTMS [63]. With respect to cocaine addiction, data have frequently been obtained from pilot controlled studies or studies with relatively small sample sizes [64, 65], and therefore are not discussed in this review. Finally, a meta-analysis on the use of TMS for all cravings in substance addiction has been published recently. With all 8 included RCTs, the authors concluded no difference between active and sham TMS for treating substance craving, regardless of the different clinical indications or TMS modalities [66]. However, when investigating subgroup analysis, active stimulation was found to be superior to sham only for trials focused on the right DLPFC.

Summary

rTMS is a safe intervention and has already shown promising effects on psychiatric disorders. However, debate still remains in issues such as how to find the optimal rTMS modality for a specific clinical indication, and the exact efficacy of rTMS for patients with treatment-resistant symptoms. Our work reviews most of the updated multicenter studies, well-designed RCTs, and meta-analyses in psychiatry to help clarify the above issues.

In our review, while HF rTMS was consistently effective in treating MDD or TRD [21, 27], LF rTMS also showed an efficacy comparable with standard venlafaxine treatment for TRD [20]. At the same time, low-field synchronized TMS, with less adverse effects than traditional HF rTMS, had a promising effect on MDD, especially TRD [22]. However, the overall effects of rTMS on TRD appeared to be small in meta-analysis with a large sample of TRD patients and did not persist for long [22]. Such results indicate that more large-sample RCTs are still needed to clarify the short-term and long-term effects of the specific rTMS modality for treating TRD. So far, evidence on the efficacy of maintenance rTMS after an acute response is equivocal [38]. Therefore the limited durability of the antidepressant effect of rTMS after acute treatment [30] may hinder its application in patients who experience recurrent depression, and a more efficient maintenance protocol should be considered in future.

In schizophrenia patients, recent meta-analyses supported an effect of LF rTMS over the left temporoparietal region on refractory auditory hallucinations and positive symptoms [41, 43], while other rTMS modalities such as prefrontal TMS, prefrontal TBS, or right-side temporoparietal TMS seemed to lack evidence for treating auditory hallucinations and positive symptoms in schizophrenia [41, 42]. Inconsistent results have been reported in recent

multicenter studies on the efficacy of rTMS for patients with prominent negative symptoms [45, 46]. Factors such as greater severity of illness and negative symptoms and relatively few stimuli or repetitive sessions might have caused the failure to demonstrate a significant effect of rTMS in patients with prominent negative symptoms [46]. On the other hand, when considering the heterogeneity and bias across RCTs in treating negative symptoms, the efficacy of HF prefrontal TMS may largely decrease, according to a recent meta-analysis [41]. As for cognitive impairment, no improvement has yet been evident in either temporoparietal or prefrontal TMS protocols [41, 49].

Accumulated RCTs, though mostly with small samples, demonstrated the efficacy of rTMS for the treatment of PTSD [50, 52]. But the optimal rTMS protocol for PTSD has still not been determined. The data on rTMS treatment for PD and GAD are relatively scarce, so no conclusions could be drawn for these conditions. As for OCD, LF rTMS over the cortico-striato-thalamo-cortical circuits, including the DLPFC, OFC, and SMA appears to be more efficient than HF rTMS [58–60]. The only evidence supporting HF rTMS to treat OCD was an αEEG-guided TMS protocol over the bilateral DLPFC [61]. Since the data were all from small-sample RCTS, future large-sample RCTs should be conducted to verify the efficacy of LF rTMS for OCD. Finally, regarding substance addiction and craving, evidence of rTMS has only been found in cigarette craving and nicotine use disorder in a recent multicenter study [62]. And the optimal protocol seemed to be HF rTMS over the prefrontal and insular cortices. While no difference between active and sham TMS for treating substance craving was found in a recent meta-analysis, subgroup analysis showed promise in active rTMS focused on the right DLPFC [66].

Overall, the application of rTMS to psychiatric disorders shows promising efficacy, especially in depression and the positive symptoms of schizophrenia. However, the effects on treatment-resistant depression, severe negative symptoms, and the cognitive symptoms of schizophrenia are still ambiguous, and need further investigation to find the optimal rTMS protocols. In addition, larger and well-designed RCTs are needed to verify the present potential effects of rTMS on other conditions such as anxiety disorders, OCD, and substance or food craving.

Acknowledgements This review was supported by grants from the National Natural Science Foundation of China (81501152 and 81671332), the National Key Basic Research and Development Program, Ministry of Science and Technology, China (2016YFC1306800, 2016YFC1306803), the Brain Project of Shanghai Jiaotong University, School of Medicine, China (2015NKX001, 15ZH2015, and W35XT), and Shanghai Hospital Development Center, China (SHDC12014111).

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