Repetitive transcranial magnetic stimulation treatment for depressive disorders: current knowledge and future directions

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Purpose of review
After three decades of clinical research on repetitive transcranial magnetic stimulation (rTMS), major depressive disorder (MDD) has proven to be the primary field of application. MDD poses a major challenge for health systems worldwide, emphasizing the need for improving clinical efficacy of existing rTMS applications and promoting the development of novel evidence-based rTMS treatment approaches.

Recent findings
Several promising new avenues have been proposed: novel stimulation patterns, targets, and coils; combinatory treatments and maintenance; and personalization and stratification of rTMS parameters, and treatment of subpopulations.

Summary
This opinion review summarizes current knowledge in the field and addresses the future direction of rTMS treatment in MDD, facilitating the establishment of this clinical intervention method as a standard treatment option and continuing to improve response and remission rates, and take the necessary steps to personalize rTMS-based treatment approaches.

Keywords
depression, efficacy, repetitive transcranial magnetic stimulation

INTRODUCTION

The worldwide burden of major depressive disorder (MDD) and the inter-individual variability in response to pharmacological interventions along with their unfavourable side-effects demand the development of new therapeutic strategies. Among them, repetitive

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## KEY POINTS

- rTMS has become an established tool to treat depression.

- To optimize response and remission rates, novel stimulation parameters and individualized treatment protocols are needed.

- The identification of personalized predictive factors may refine and improve the rTMS therapeutic potential.

transcranial magnetic stimulation (rTMS) has undergone intensive research leading to its approval by the FDA as a therapy for treatment-resistant depression (TRD) in 2008. rTMS is now an approved treatment for MDD in many countries and is being considered a first-line treatment according to recent North American and European guidelines [1,2].

The most prominent rTMS target area in MDD, the dorsolateral prefrontal cortex (DLPFC) – a key hub of the frontoparietal network – has been implicated in the regulation of a multitude of processes such as decision-making, working memory, and attention, and this region has been found to be hypoactive when clinically depressed [3]. Hypoconnectivity of the frontoparietal network is associated with hyperconnectivity of the default mode network, which may promote negative emotional bias, dysfunctional self-referential processing, and rumination [4]. By stimulating the left DLPFC, high-frequency (HF)-rTMS has been suggested to normalize the functional balance between neural networks, for example, down-regulate connectivity within the default mode network, the left DLPFC and insula, and between the salience network and the hippocampus, which was associated with improvement of depressive symptoms [5,6]. As visualized in Fig. 1, response and remission to rTMS alone (monotherapy) has
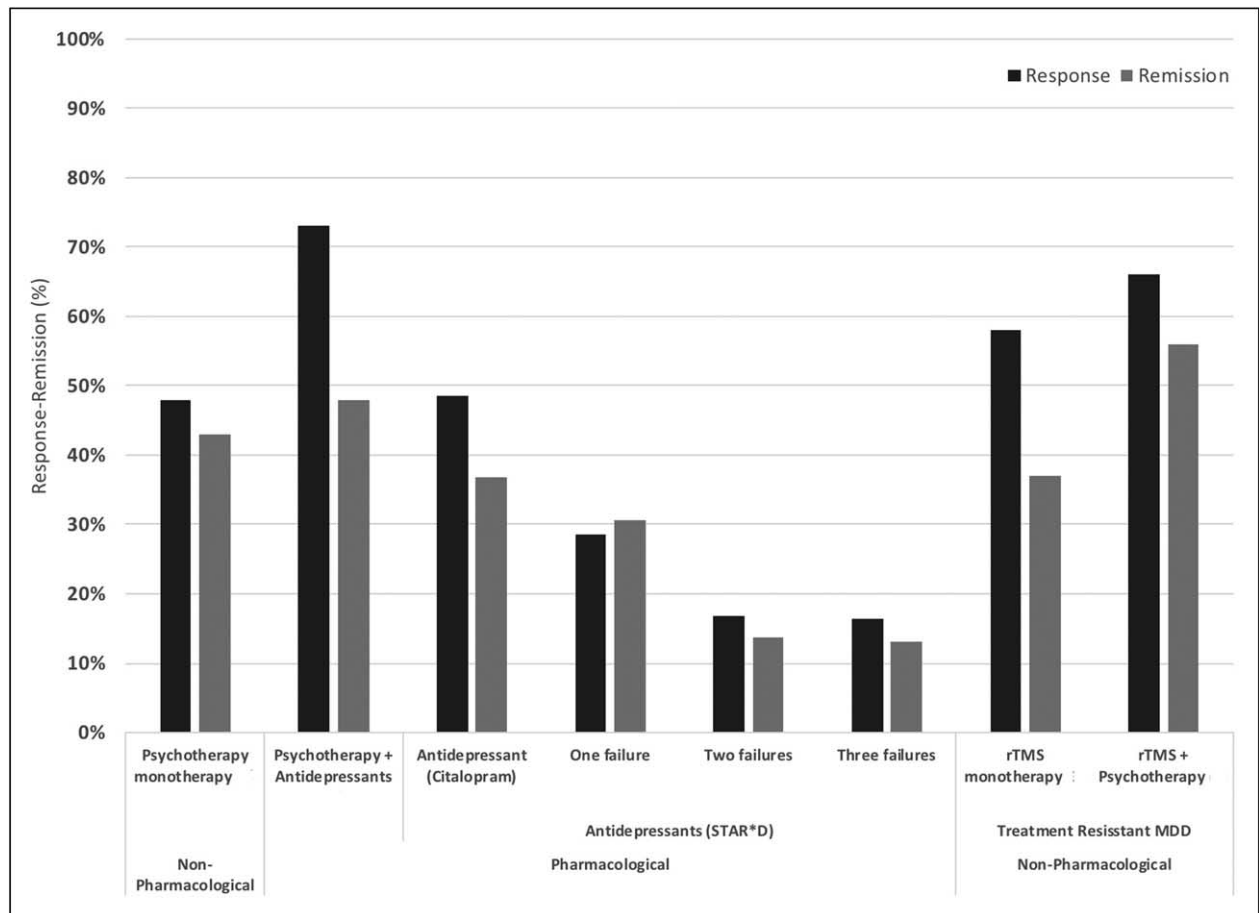
FIGURE 1. Response and remission rates of various monotherapeutic and combinatory antidepressant treatments based on the largest studies and datasets available. psychotherapy monotherapy, psychotherapy and antidepressants, antidepressants as first line, after one, two, and three treatment failures from the STAR*D trial, rTMS monotherapy, and rTMS combined with psychotherapy. Note the relative increase in response and remission rates for rTMS, especially relative to patients that have had two or three prior treatment failures (i.e. treatment-resistant depression), which is the typical population rTMS treatment is currently indicated for. MDD, major depressive disorder; rTMS, repetitive transcranial magnetic stimulation. Source: Adapted with permission from Refs. [27–30,49].

similar efficacy compared to antidepressant medication (monotherapy) in populations receiving medication or psychotherapy as a first-line treatment. Nevertheless, worldwide researchers are focused to increase response and remission rates for the depressed patient.

In this opinion review, we summarize findings from trials focusing on the efficacy of rTMS in MDD and discuss ongoing research and future directions on novel stimulation patterns, targets, and coils; combinatory treatments and maintenance; and personalized and stratified treatment as an avenue to precision medicine.

NOVEL STIMULATION PATTERNS, TARGETS, AND COILS

One direction involves the further development of novel stimulation patterns such as accelerated rTMS (arTMS) protocols to achieve a faster response. Moreover, increasing knowledge on network interactions and underlying neuronal mechanisms of MDD is stimulating research into novel stimulation targets, including deeper brain structures that can be reached with more adapted coil designs.

Intensifying repetitive transcranial magnetic stimulation protocols

Recent studies on rapid-acting antidepressants such as ketamine and sleep-deprivation have changed our view on how rapid antidepressant effects can take place, which has resulted in the application of arTMS. arTMS is a novel stimulation protocol that applies multiple daily sessions (with at least 600 pulses per session), hereby reducing the total treatment time [7]. From a clinical perspective, it was also introduced to challenge response and remission rates as observed with electroconvulsive therapy (ECT). Using excitatory stimulation paradigms over the left DLPFC, accelerated high frequency (aHF) rTMS and accelerated intermittent theta burst stimulation (aiTBS) yield similar remission and response rates as daily rTMS, but not of ECT [8]. Increasing the number of rTMS sessions over the left DLPFC – from one to two sessions a day – further improves clinical outcome [9] and reduces treatment time [10]. Furthermore, increasing the number of stimulation sessions over the dorsomedial PFC (dmPFC) is associated with a similar clinical response, adding to a significantly faster onset [11]. This not only agrees with clinical observations using aHF-rTMS [7] and aiTBS [12▪], but also with a recent pilot study [13] showing that high-dose aHF-rTMS (i.e., 10 sessions per day) over the left DLPFC for 5 days results in acute response and remission in high TRD.

These recent findings underline the value of novel protocols in terms of a much faster alleviation of depression symptoms. The most important clinical challenge will therefore be to validate and further optimize the stimulation parameters while still reaching comparable response and remission rates at or beyond the level that is observed with ECT.

Repetitive transcranial magnetic stimulation coil positioning

Slight changes in coil positioning can lead to large variations in the underlying brain regions that are stimulated. It is therefore crucial to reliably stimulate these identified targets throughout the treatment period. Different coil positioning approaches are used, with varying levels of cost vs. clinical effectiveness. These include the 5-cm-rule; stimulation over F3; and neuronavigated stimulation. The 5-cm-rule is the simplest approach. However, this approach has been criticized for not accounting for inter-individual differences in brain anatomy or even head size. Stimulation over F3 addresses this latter limitation. Here, the TMS coil is positioned at EEG electrode position F3, which is assumed to correspond to the DLPFC. The most optimal personalized coil positioning approach is based on frameless stereotactic systems, allowing precise (online) neuronavigation of a predefined brain area, either based on patients' own neuroimaging data or a template. When it comes to precision, the superiority of using TMS neuronavigation is undisputed in research. However, the question whether it also increases clinical efficacy in depression treatment, remains a matter of debate [14]. Despite encouraging findings [15], the absence of a clear anatomical criterion to define the optimal brain target keeps the uncertainty around the clinical relevance of precision using neuronavigation [16]. Future clinical research may do well to conduct large controlled noninferiority rTMS treatment studies comparing the different localization methods and their relation to superior clinical outcomes.

New coil types

Instead of older circular coils or the more focused figure-of-eight coils, the double-cone coil features two windings that are set apart at a defined angle, which is thought to allow modulation of deeper brain areas such as the dorsomedial prefrontal cortex (dmPFC) or anterior cingulate. Its specific geometry is thought to lead to higher current in the central fissure resulting in a more efficient stimulation of the dmPFC. The rationale behind this approach lies in the involvement of the dmPFC in

affective, sensory autonomic, cognitive, and salience regulation. The current available literature is promising on this approach, although independent replication and head-to-head comparisons in placebo-controlled studies are needed.

The 'H-coil' has been developed to stimulate deeper brain regions of 4–6 cm than the traditionally used coils (figure-of-eight/circular coils), and was therefore introduced as deep TMS (dTMS). Based on phantom measurements, however, it is clear that H-coils (e.g. the H1-coil for depression) also provide less focal stimulation following the well-known trade-off between depth (or intensity) and focality of TMS [17]. In 2013, the FDA approved the first dTMS device (with an H1-coil) for the treatment of depressed patients who had failed to respond to antidepressant in their current episode based on the study by Levkovitz and colleagues [18■■]. In this RCT with 212 MDD outpatients, remission rates were higher in the dTMS than in the sham group (HDRS – remission: 32.6 vs. 14.6%) and were stable during the 12-week maintenance phase. Also, recent studies suggest that a significant proportion of MDD patients (61%) who did not reach response after 4-weeks of dTMS treatment benefit from a continuation treatment at a lower frequency of weekly dTMS sessions [19]. An open study [20] combining dTMS with selective serotonin reuptake inhibitors in a population that failed to respond to either selective serotonin reuptake inhibitor alone or dTMS alone showed 35.3% response and remission rates. dTMS moreover appears to be well tolerated and efficacious in late-life depression [21], and showed to be potentially effective as add-on treatment in resistant bipolar depressed patients [22]. Till date, randomized head-to-head comparisons of effectiveness between the H-coil and figure-of-eight coils are still lacking.

COMBINATORY TREATMENTS AND MAINTENANCE

The rationale behind combining rTMS with other treatment approaches lies in the assumption that concomitant stimulation on different levels (i.e. physiological, cognitive, affective, and behavioural) may result in synergistic effects.

Combining repetitive transcranial magnetic stimulation with psychopharmacotherapy

Generally, patients undergoing rTMS continue to receive antidepressants. However, little is known about the impact of pharmacotherapy on rTMS efficacy. Preclinical studies suggest that anti-depressants, anticonvulsants, and benzodiazepines

influence cortical excitability. In humans, antide-pressants appear to facilitate neuroplastic effects of brain stimulation, whereas anticonvulsants and benzodiazepines seem to have an inhibitory effect [23]. So far, rTMS studies in MDD are very heterogeneous concerning concomitant pharmacotherapy precluding a comparison and therefore determination of a superior combinatory effect of any of these approaches. In some studies, patients were unmedicated, whereas in others, only benzodiazepines or other specific antidepressant medications were allowed during rTMS treatment. And in a few studies, medication could be freely chosen, but had to be kept stable. Consequently, potential interactions of specific pharmacological regimes and rTMS can neither be excluded nor exploited to achieve better clinical outcomes. Future research investigating the impact of antidepressants on rTMS efficacy – including possible synergistic effects – is highly desirable.

Combining repetitive transcranial magnetic stimulation with psychotherapy

Within a naturalistic setting, rTMS can be considered an effective treatment and clinical benefit appears to translate well to clinical practice. Additionally, in combination with psychotherapy, response and remission rates may have the potential to increase further and sustain durable effects. In a large naturalistic study, Donse and colleagues [24■] reported that the simultaneous application of rTMS and psychotherapy in TRD resulted in a 66% response and a 56% remission rate at the end of treatment with 60% sustained remission at a 6-month follow-up [24■,25–27] (Fig. 1). Interestingly, early symptom improvement (at session 10) was highly predictive of response and may therefore be used to guide rTMS and psychotherapy continuation. Though promising, randomized controlled clinical trials as well as systematic research on combined rTMS-psychotherapy approaches are needed.

Combining repetitive transcranial magnetic stimulation with cognitive training

Cognitive impairments can be observed in over 50% of depressed patients but remains highly undertreated. A recent meta-analysis investigating cognitive enhancing effects of rTMS alone found a modest improvement in performance of the Trail Making Test, a test that draws on psychomotor speed, visual scanning, and cognitive flexibility [28]. Cognitive training used on its own seems promising [29]. The combined application of both methods, however, might be key for cognitive enhancing effects. It has

been argued that without cognitively relevant brain activity, rTMS would not fall on fruitful ground and therefore not result in cognitive improvement. Given that patients are usually unengaged during rTMS treatment, it would be feasible to add cognitive training. Future studies should therefore explore whether such a multimodal approach can lead to a sustained reduction in depressive symptoms and additionally may enhance cognition. It goes without saying that to fully unveil cognitive effects, a broad range of cognitive functions should be assessed with valid, reliable, and sensitive methods.

Future studies should moreover investigate the value of multiple combined approaches, such as the ones outlined above, and find out whether synergies can be exploited to further enhance clinical outcomes.

Maintenance repetitive transcranial magnetic stimulation

Although there are no clear guidelines to date, maintenance rTMS (mTMS) is used after successful response to an acute course of rTMS and has been suggested to prolong its positive clinical effects. Nevertheless, studies are highly heterogeneous in terms of design, with rather small sample sizes, and lacking placebo controls. The frequency of mTMS varies from distributed single sessions (weekly, biweekly, bimonthly, or monthly) spread over 2–3 months, to short treatment periods of daily mTMS (e.g. 1 week per month) or so called clustered mTMS (e.g., five sessions over a two-and-a-half-day period per month or every 5th week) applied over 1, 2, 3, 9, and 12 months and up to several years. Nonetheless, most patients show moderate/marked benefits with mTMS compared to no treatment, achieving remission for up to 3 months to 5 years [30–33]. Future studies should investigate the capacity of mTMS to prevent relapses and evaluate its long-term safety and efficacy.

PERSONALIZED AND STRATIFIED TREATMENT AS AN AVENUE TO PRECISION MEDICINE

Personalized treatment

In a recent network meta-analysis, the efficacy and tolerability of eight rTMS modalities and sham, including 81 studies and 4233 patients, was evaluated. Some rTMS strategies are more effective than sham [34▪▪], but no active rTMS strategy was significantly superior. However, a striking dichotomy becomes evident with the majority of rTMS protocols. Although a considerable number of patients respond, an even slightly larger number of patients

do not. Future rTMS research should focus on the inter-individual variability of effects [35], and promote the establishment of personalized rTMS treatment: tailoring rTMS to individualized targets and predictors based on structural or functional connectivity [36,37▪]; and adjusting rTMS protocols to distinct brain states guided by individual neurophysiological markers or using closed-loop protocols [38▪,39]. Furthermore, cognitive indices could be leveraged for several purposes: baseline cognitive performance can predict response to rTMS [40] and therefore – based on machine learning approaches – could be used as a relatively straightforward method for prediction; cognitive changes can provide insights on rTMS mechanisms of action, for instance, by exploring whether they mediate depression improvement [41].

In the future, individualized rTMS treatment may become an interesting case for precision medicine, particularly as novel paradigms could show that rTMS involves the respective individual target whether these are circuits, brain states, or both [42].

Stratified treatment

A complementary approach for increasing precision in psychiatry is based on machine-learning approaches and other advanced statistics. In the rTMS field, such approaches have been conducted for symptom clustering and to define subtypes of MDD. Based on clustering according to anxiety and anhedonia dimensions and associated resting state functional magnetic resonance imaging connectivity patterns, Drysdale and colleagues [43▪▪] identified and validated four biotypes of which two were more responsive to rTMS than the others. In contrast to standard protocols, however, rTMS was applied over the DMPFC using a double-cone coil. Furthermore, a very recent study failed to replicate the biotype solution of the prior report [44]. Kaster *et al.* [45] published a secondary analysis of a noninferiority trial comparing 10 Hz rTMS and intermittant Theta Burst Stimulation applying group-based trajectory modelling. Four response trajectories were identified: nonresponse; rapid response; higher baseline symptoms-linear response; and lower baseline symptoms-linear response. The nonresponse trajectory was associated with higher depression scores at baseline, and the rapid response trajectory with older age, lower depression scores (i.e. self-rating), and lack of benzodiazepine use.

Treatment of subpopulations

Knowledge about the relevance of the type of depression for rTMS efficacy is rather limited. In

many rTMS studies, patients with both unipolar and bipolar disorder were included, without resulting in any clear indication of differential response. Notably, out of four RCTs [46–49] that included only patients with bipolar disorder, only one was positive [46].

rTMS seems especially suited for the treatment of patients with contraindications for pharmacologic treatment, for example pregnant and breast-feeding women, or patients with multimedication or comorbid somatic disorders. Several case reports and three studies have suggested that rTMS is efficient in reducing depressive symptoms during pregnancy. Importantly, no negative pregnancy or foetal outcomes were found except for the potential association with preterm birth and mild headache for mothers [50,51]. For patients with MDD and Parkinson's disease, a recent meta-analysis has shown clear antidepressant efficacy of rTMS [52] indicating that medical comorbidities have no negative influence on the antidepressant efficacy of rTMS. Similarly, elderly patients with depression seem to respond well to rTMS [53].

CONCLUSION

Although rTMS is an approved and acknowledged treatment for MDD, the clinical field is rapidly evolving, aiming to optimize response and remission rates for MDD patients. New studies are emerging, evaluating novel stimulation parameters and fine tuning individualized treatment protocols. Notwithstanding – apart from the need for a deeper understanding of its mechanisms of action – there remain substantial unanswered questions such as the stability of the medium to long-term antidepressant effects of this technique, the optimal sequencing between rTMS sessions, the combination with other antidepressant treatments, or the putative role of rTMS as a cognitive enhancer. The identification of personalized predictive factors of response also continues to be an important issue to refine and improve the rTMS therapeutic potential.

Conflicts of interest
There are no conflicts of interest.

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