The Effects of Repetitive Transcranial Magnetic Stimulation on Cognitive Performance in Treatment-Resistant Depression. A Systematic Review

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Key Words

Repetitive transcranial magnetic stimulation · Noninvasive brain stimulation techniques · Neurocognition · Treatment-resistant depression · Major depressive disorder

Abstract

Background: Major depressive disorder (MDD) is a disabling illness associated with significant functional and psychosocial impairment. Although many psychopharmacological agents are currently available for its treatment, many MDD patients suffer from treatment-resistant depression (TRD). **Methods:** A systematic review of the current literature (Pubmed/Medline, Scopus and ScienceDirect search) has been conducted with the primary aim to investigate the role of repetitive transcranial magnetic stimulation (rTMS) in improving neurocognition in patients with TRD. Studies were included according to the following criteria: (a) being an original paper in a peer-reviewed journal and (b) having analyzed the effect of rTMS on neurocognitive functioning in TRD. **Results:** The combined search strategy yielded a total of 91 articles, of which, after a complete analysis, 22 fulfilled our inclusion criteria. Based on the main findings, most of the selected studies suggested the existence of a trend towards

improvements in the neurocognitive profile using rTMS. Negative findings have also been reported. However, most studies were limited by their small sample size or included mixed samples, or the adopted single-blind designs potentially biased the blinding of the study design. **Conclusion:** rTMS is a noninvasive brain stimulation that may be considered a valuable and promising technique for cognitive enhancement in TRD.

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Introduction

Major depressive disorder (MDD) is a common and disabling illness associated with significant functional and psychosocial impairment [1]. Patients with MDD usually experience frequent relapses, incomplete recovery between episodes and persistent dysfunction in daily life [2]. Although many psychopharmacological agents are currently available for its treatment [3], MDD is also associated with an increased risk for suicidal behaviors [4–6].

Currently, 60–70% of patients affected by MDD will ultimately respond to trials of standard medication and

psychotherapy treatments [7]; therefore, there are still approximately 30% of MDD patients who fail to respond adequately to the available antidepressant treatments [8]. These patients with a treatment-resistant depression (TRD) commonly report a significant decline in daily functioning together with an increased risk of functional impairment and mortality [9]. In the United States, TRD has a prevalence of >1% and has been reported as a high-cost and disabling disorder [10, 11].

The Food and Drug Administration (FDA) has approved repetitive transcranial magnetic stimulation (rTMS) for the treatment of both MDD and TRD in adolescent and adult populations. rTMS has been reported to act on brain areas involved in the pathogenesis of MDD [12, 13].

Based on functional neuroimaging studies in depressed subjects, a reduced activity in the left prefrontal cortex (in particular in Brodmann areas BA 9 and BA 46) and an altered activation in a corticosubcortical network including the subgenual and anterior cingulate cortices have been reported [14]. Therefore, rTMS studies tested the hypothesis to increase the activity over the left dorsolateral prefrontal cortex (DLPFC) using high-frequency rTMS over both acute and long-term periods [15–18]. Other mechanisms have been proposed. Decreasing the right DLPFC activity via low-frequency rTMS has also been reported to be effective, presumably due to the increased activity in left DLPFC by way of transcallosal connections or due to a reduction in right DLPFC activity. Meta-analytic studies have shown that high-frequency (5–20 Hz) rTMS of the DLPFC may be an effective antidepressant treatment with a moderate-to-large effect size [19–22].

Several randomized, sham-controlled trials designated to investigate the antidepressant efficacy of rTMS also reported interesting findings regarding the effects of rTMS on cognitive performance [12, 23–34]. However, given the limited availability of neurocognitive measures and the open nature of most available studies, to what extent rTMS may be really beneficial on neurocognitive performance is still unknown.

This systematic review of the current literature is aimed to systematically investigate the role of rTMS in improving neurocognition in patients with TRD.

Methods

Information Sources, Search Strategy and Study Selection

A detailed search strategy summarized in figure 1 was used to identify relevant studies. In order to provide a timely systematic review of rTMS changes on neurocognition in TRD patients, we

Fig. 1. Flowchart of the search and selection process. The present figure summarizes the search strategy used for selecting studies (identification, screening, eligibility, inclusion process) in this review.

performed a detailed Pubmed/Medline, Scopus and ScienceDirect search to identify all papers and book chapters in English during the period between 1995 and January 2014.

The search used a combination of the following terms: ‘repetitive transcranial magnetic stimulation’ OR ‘rTMS’ AND ‘neurocognition’ OR ‘neurocognitive performance’ OR ‘cognitive effects’ OR ‘cognitive adaptation’ AND ‘treatment-resistant depression’ OR ‘refractory depression’ OR ‘TRD’. Where a title or abstract seemed to describe a study eligible for inclusion, the full text article was examined to assess its relevance based on the inclusion criteria. Two independent researchers conducted a 2-step literature search. Any discrepancies between the two reviewers who, blind to each other, examined the studies for their possible inclusion were resolved by consultations with two senior authors. The reference lists of the articles included in the review were also manually checked for relevant studies. All English-language full-text articles reporting original data about the main topic were included.

Studies were included according to the following criteria: (a) being an original paper in a peer-reviewed journal and (b) having analyzed the effect of rTMS on neurocognitive functioning in TRD. Figure 1 summarizes the search strategy used for selecting studies (identification, screening, eligibility, inclusion process) in the present review.

Study Design and Eligibility Criteria

To achieve a high standard of reporting, we adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [35]. The PRISMA Statement consists of a 27-item checklist and a 4-phase flow diagram for reporting in systematic reviews and meta-analyses. PRISMA includes the broader effort to improve the reporting of different types of health research and, in turn, to improve the quality of research used in decision making in health care.

Recorded Variables

The recorded variables for each article about rTMS and neurocognition in TRD were sample characteristics, study design, treatment-resistant definition, brain region changes, main findings on cognition, limitations and conclusions (table 1).

Results

Number of Studies Selected

The combined search strategy yielded a total of 91 articles of which, after a complete analysis, 52 full-text articles were screened and 49 were excluded. We excluded articles not published in peer-reviewed journals and not in English, articles without abstracts, abstracts that did not explicitly mention the neurocognitive effects of rTMS in TRD patients, articles with a publication date before 1990 and those with unclear data concerning the materials and methods and the number of patients analyzed. We assessed 30 articles for eligibility, but 8 full-text articles were excluded due to low relevance to the main theme, leaving 22 articles that fulfilled our inclusion criteria and included a total of 659 patients.

Type of Studies Selected

Longitudinal Follow-Up rTMS Studies Targeting Deeper Brain Regions and Hippocampus/Related Structures

Two longitudinal follow-up studies were conducted to test the neurocognitive effects of rTMS in TRD patients. Based on the main studies which were included in the present review, one study found positive findings supporting the association between rTMS treatment and neurocognition, and one study reported negative results.

The first study by Furtado et al. [36] reported that there was no difference in pretreatment neurocognitive profiles and medial temporal lobe volumes between treatment responders and nonresponders in a total sample of 46 TRD patients. Smaller pretreatment left hippocampal volume showed only a trend towards predicting eventual subjective improvement in depressive symptomatology.

Table 1. rTMS follow-up studies investigating cognitive effects in TRD patients

Study [Ref.], year	Sample characteristics	Study design	Procedure	Location of stimulation	Cognitive domains measured and outcome instruments	Cognitive assessments	Main findings	Limitations	Conclusions
Furtado et al. [36], 2013	29 TRD patients	3-week follow-up study	MRI and neurocognitive assessments were conducted prior to rTMS treatment (baseline) and at 3 months after baseline (end point)	Hippocampus and related structures	Premorbid IQ (WTAR); visual learning and memory (BVMET); verbal learning and memory (RAVLT); speed of processing (TMT A); attention and working memory (digit span, forwards and backwards, subtest from the WAIS-III); executive functions (COWAT, TMT B, Stroop)	Baseline; end point (after 6 weeks of TMS)	An increased (although not significantly) left amygdala volume was found associated with antidepressant response, whereas a significant reduction in left hippocampus volumes from baseline was observed in nonresponders. No cognitive deterioration following rTMS treatment	The small sample size did not allow the generalization of findings	rTMS may promote neurogenesis and enhance neuronal plasticity in patients with TRD
Mayer et al. [37], 2012	9 TRD adolescent patients	3-year follow-up study	Reassessment of 8 (among the initial 9) subjects who had participated in an open-label rTMS study	Not specified	Cambridge Neuropsychological Test Automated Battery	Pretreatment; inter-treatment; end point (after 3 years of treatment)	No evidence of deterioration in symptoms of depression or cognitive functioning compared to the last assessment after rTMS	The very small sample size did not allow the generalization of findings	Improvements induced by rTMS treatment in adolescent resistant depression may be maintained in the long-term period

BVMET = Brief Visuospatial Memory Test; COWAT = Controlled Oral Word Association Test; MRI = magnetic resonance imaging; RAVLT = Rey Auditory Verbal Learning Test; TMT A = Trail Making Test A; TMT B = Trail Making Test B; WAIS-III = Wechsler Adult Intelligence Scale – Third Edition; WTAR = Wechsler Test of Adult Reading.

The second study by Mayer et al. [37] suggested that improvements induced by rTMS treatment in adolescent resistant depression may be maintained in the long-term period. In particular, no evidence of deterioration in depressive symptoms or cognitive functioning was found compared to the last assessment after rTMS.

Randomized Sham-Control and Crossover Placebo-Controlled Double-Blind Studies and Post Hoc Analysis rTMS Studies Targeting the Left DLPFC

Eight randomized sham-control and crossover placebo-controlled double-blind studies using rTMS targeting the left DLPFC were conducted to test the neurocognitive effects of rTMS in TRD patients. According to the main studies included in the present review, 6 studies reported positive findings supporting the association between rTMS treatment and neurocognition, whereas 2 studies reported negative results.

The first was the study by Hoy et al. [38] who found in a post hoc analysis of the cognitive data derived from 4 clinical trials using rTMS that the reduction of depression severity was associated with initial improvements in terms of immediate visuospatial memory in a total sample of 137 TRD patients. The authors stated that after regression analyses, visuospatial improvement was found as a significant predictor of the degree of eventual improvement.

Vanderhasselt et al. [39] conducted a crossover placebo-controlled double-blind study on 15 TRD patients and found that, after 2 weeks of high-frequency rTMS, depressive symptoms improved in 53% of patients. Significantly, mood did not improve after a single session, but attentional control was increased only within TRD patients.

Fitzgerald et al. [40] also reported significant overall improvements in immediate verbal memory and verbal fluency independently of the type of rTMS received in a 2-arm randomized double-blind study on a sample of 27 TRD patients.

Conversely, McLoughlin et al. [41] found no Hamilton Rating Scale for Depression (HRSD) difference before or after treatment on global measures of cognition and quality-adjusted life years at 6 months between the 2 patient groups in a sample of 46 TRD patients who were randomized to receive rTMS or electroconvulsive (ECT) treatments.

Similarly, Rosa et al. [42] suggested that there was no difference in terms of neuropsychological test performance between 42 TRD patients aged between 18 and 65 years who were randomly assigned to receive either rTMS or ECT.

The response and remission rates for the TMS group were indeed significantly greater for those patients who were treated with rTMS than for the sham group in the study by Avery et al. [23]. The authors reported that both treatment groups showed significant improvements in cognitive functioning at follow-up, but no significant differences regarding any of the neuropsychological test measures were reported between the groups.

Improvements in long-term memory recall and recognition were also found in 30 TRD patients treated with rTMS as suggested by Schulze-Rauschenbach et al. [43]. In the rTMS group, some objective memory measures and subjective memory rating were found to improve in parallel with the improvement in mood up to normal performance levels.

Lastly, Padberg et al. [25] reported together with a mild significant reduction of depressive symptoms improvements in verbal memory (e.g. verbal learning task) of 18 TRD patients after slow rTMS.

Specifically, there was a statistically significant time $\times$ group interaction with improvement of verbal memory performance after performing fast rTMS.

Randomized Controlled Double-Blind rTMS Studies Targeting the Anterior Middle Frontal Gyrus

Two randomized controlled double-blind studies were conducted using rTMS targeting of the anterior middle frontal gyrus in TRD patients [28, 44]. Overall, one study [28] supported the association between rTMS treatment and neurocognition, whereas the other [44] did not sustain such an association. Except for the main location of stimulation, these studies did not significantly differ from the studies of the previous section.

In the first study, a significant reduction of depressive symptoms was reported in a sample of 20 patients with poststroke depression [44]. According to this study, there were no significant changes in cognitive functioning between the active and the sham stimulation groups.

Also, Moser et al. [28] reported that 19 middle-aged/elderly TRD patients in the active rTMS group improved significantly on a test of cognitive flexibility and conceptual tracking. Therefore, rTMS targeted at the anterior portion of the left middle frontal gyrus may be associated with cognitive improvements as assessed by Trail Making Test B.

Open-Label rTMS Studies Targeting the Right and Left DLPFC

Nine rTMS open-label studies targeting the right and left DLPFC analyzed the neurocognitive effects of rTMS in TRD patients. Based on the main studies included in

the present review, 7 studies [45–51] reported positive findings supporting the association between rTMS treatment and neurocognition, whereas one study [52] suggested the existence of only a trend towards improvements in the neurocognitive profile using rTMS, and another study [53] found no difference in the neurocognitive profiles of those who were treatment responders and those who were nonresponders to rTMS treatment.

The first is the study of Pallanti et al. [52] who found that low-frequency rTMS appeared effective in 42.9% of depressive resistant subjects, but the performances regarding the Corsi test and phonemic verbal fluency were improved independently from depressive symptoms variation. A significantly reduced left hemisphere resting motor threshold was registered at the end of the rTMS protocol. However, only a trend for improvement in cognitive function was found in this study independently from clinical response.

Also, Furtado et al. [53] reported that in a sample of 46 TRD patients there was no difference in the pretreatment neurocognitive profiles and medial temporal lobe volumes between those patients who were treatment responders and those who were nonresponders.

Other open-label studies were conducted to test the neurocognitive effects of rTMS on TRD sustaining the positive effects of rTMS on neurocognition. Kedzior et al. [45] reported a significant improvement in immediate memory as assessed by the Repeatable Battery for the Assessment of Neuropsychological Status and a reduction in depressive scores from baseline to the end of the study in 10 TRD patients who performed significantly better on the concept-shift ability after rTMS when compared with 8 healthy volunteers.

Similarly, Holtzheimer et al. [46], who conducted an open-label accelerated TMS consisting of 15 rTMS sessions administered over 2 days on 14 TRD depressed patients, found that neuropsychological function did not decline with treatment and showed persistent improvement at week 6.

Lower levels of depression as measured by the Beck Depression Inventory and Child Depression Rating Scale and improvements in reaction time (immediate and at 1 month) and planning (at 1 month) were also found by Bloch et al. [47]. The authors concluded that rTMS could be a possible therapeutic option for adolescent depression.

Significant antidepressant effects within 2 weeks in both sham and real stimulation groups were also reported by Mosimann et al. [48] in another open-label study. However, the authors stated that there were no differ-

ences between those patients who received sham and those who received real stimulation in terms of antidepressant effects and cognitive improvements concerning the Mini-Mental Status Examination performance, memory and executive and attentional functions.

Furthermore, Fabre et al. [49] reported that 45.4% of patients in their sample of 11 subjects with late-onset resistant vascular depression were responders, and specific improvements in verbal fluency and visuospatial memory were reported after 2 weeks of rTMS. Also, concerning verbal memory, the delayed recall was significantly reduced in the responders' group.

A modest but significant improvement in working memory, executive function, objective memory and fine motor speed domains was reported by Martis et al. [50] but, interestingly, the significant improvements in executive functions could not be explained by improved mood. The authors added that no adverse neurocognitive changes emerged over the period from baseline to after the rTMS period.

Finally, Triggs et al. [51] found that rTMS had no adverse effects on neuropsychological performance together with a persistent (at 1 and 3 months later) antidepressant effect as measured by the HDRS and Beck Depression Inventory total scores in a sample of 10 TRD patients. Also, rTMS treatments were associated with significant reductions in the motor evoked potential threshold in 90% of patients who remained off psychotropic medications during the 2-week treatment period.

Open-Label rTMS Studies Targeting Deeper Brain Regions Over the Prefrontal Cortex

Based on the main results of the present review, only one open-label study using rTMS targeting deeper brain regions over the prefrontal cortex was conducted to test the neurocognitive effects of rTMS in TRD patients. In this study, Levkovitz et al. [54] found a greater improvement in HDRS scores in 65 medication-free depressive resistant patients with the use of high-stimulation intensity compared with low-stimulation intensity. The authors reported that no negative impact on cognition was observed. Also, patients who were significantly impaired at baseline regarding sustained attention (as measured by the Rapid Visual Processing task), visuospatial memory (as evaluated by the Paired Associated Learning task), cognitive planning (as assessed using the Stockings of Cambridge task) and spatial memory (as measured by the Spatial Working Memory task) normalized over time, especially in the groups receiving deep left lateralized treatments.

Discussion

This systematic review of the current literature is mainly aimed to investigate the role of rTMS in improving neurocognitive performance in patients with TRD.

Based on the main findings, most (16) of the selected studies [23, 25, 28, 37–40, 43, 45–51, 54] supported the association between rTMS and neurocognitive effects; only two studies [52, 53] suggested the existence of a trend towards improvements in neurocognitive profile using rTMS, and some (4) studies [36, 41, 42, 44] did not confirm this association (tables 1–3).

Overall, most of the mentioned studies on TRD samples were conducted over the DLPFC. The rationale of this target is mainly related to the altered cortical metabolism as well as abnormal neurotransmission of this brain region that seems to be involved in the pathogenesis of some depressive symptoms and cognitive dysfunctions [55, 56]. The DLPFC is a crucial brain region for neurocognitive performance (e.g. attention, memory, executive functions, psychomotor speed and social cognition) as it is neuroanatomically connected with frontosubcortical brain areas, the dysfunctions of which are largely involved in many neuropsychiatric diseases [57].

Stimulation of the DLPFC is significantly associated with enhanced neurocognition although a substantial effect in all neurocognitive domains has not been clearly demonstrated. Overall, improvements in verbal memory have been more frequently reported independently of clinical effects, whereas specific improvements in verbal learning, verbal memory and psychomotor speed seem to be more closely associated with clinical improvements [58]. Also, based on the main results of the present review, variable rTMS improvements may be induced regarding psychomotor speed, attention, verbal fluency, executive function and working memory domains.

Other brain regions have been proposed as alternative targets for rTMS. There are studies targeting nonconventional brain regions such as deeper brain regions and hippocampus-related structures [36, 54, 59] and anterior middle frontal gyrus [28, 44] associated with positive results both in terms of general depressive symptoms and neurocognitive improvements.

Specifically, the stimulation of deeper brain regions has been associated with rapid (4 weeks of treatment) and prolonged (18 weeks of treatment) antidepressant effects [59]; the stimulation of hippocampus-related structures (e.g. amygdala) has been linked with enhanced neurogenesis and neuronal plasticity together with increased antidepressant response in patients with TRD [36], whereas

the stimulation of the anterior portion of the left middle frontal gyrus has been proposed as an alternative rTMS target associated with cognitive improvements that may be assessed using Trail Making Test B [28].

Among the selected studies, not all reported significant differences between active and sham rTMS groups concerning neurocognitive effects [36, 41, 42, 44]. Furtado et al. [36] reported that there was no difference in the pretreatment neurocognitive profiles and medial temporal lobe volumes between treatment responders and non-responders in a total sample of 46 TRD patients. In their study, smaller pretreatment left hippocampal volume showed only a trend towards predicting eventual subjective improvement in depressive symptomatology. However, this study was mainly conducted to investigate the potential of rTMS in inducing neurogenesis and enhancing neuronal plasticity.

In another study, McLoughlin et al. [41] also reported no HRSD difference before or after treatment on global measures of cognition and quality-adjusted life years in a selected sample of 46 TRD patients. The authors found no differences between patient groups at 6 months who were randomized to receive rTMS or ECT treatments. Furthermore, Rosa et al. [42] suggested that there was no difference in terms of antidepressant efficacy between 42 TRD patients treated with ECT and those with rTMS, although response and remission rates were relatively low for both treatments. The authors stated that there was no significant difference in the neuropsychological test performance after these treatments. However, the two mentioned studies are limited by the fact that they adopted a randomized single-blind study, potentially biasing the blinding of the design as suggested by the same authors.

Other negative findings have been reported. A significant reduction of depressive symptoms was found in a sample of 20 patients with poststroke depression [44]. According to this study, there were no significant changes in cognitive functioning between the active and the sham stimulation groups. However, the small sample size and the selection of a mixed sample (both unipolar and bipolar poststroke depression patients) restrict the statistical power of the study and increase the probability of a type II error.

Some authors [60] suggested that the positive effects of rTMS on the cognitive functioning depend on the paradigms that were investigated and the rTMS parameters that were used in the different studies; therefore, these positive effects are not observed in all studies.

According to the current mixed findings, it is difficult to speculate about the mechanism underlying the im-

Table 2. rTMS randomized sham-control, crossover placebo-controlled double-blind studies and post hoc analyses investigating cognitive effects in TRD patients

Study [Ref.], year	Sample characteristics	Study design	Procedure	Location of stimulation	Cognitive domains measured and outcome instruments	Cognitive assessments	Main findings	Limitations	Conclusions
Hoy et al. [38], 2012	137 TRD patients	Post hoc analysis of the cognitive data derived by 4 clinical trials using rTMS	Trials using rTMS had a duration of 6 weeks	Study 1 = right or left DLPFC; study 2 = left DLPFC; study 3 = sequential bilateral DLPFC; study 4 = sequential bilateral or left DLPFC	Attention (digit span forward); working memory (digit span backward); immediate and delayed verbal memory (HVLT); immediate and delayed visuospatial memory (BVRT); verbal fluency (COWAT)	Baseline; after 2 or 3 weeks of rTMS; end point (after 4 or 6 weeks of treatment)	The reduction of depression severity was associated with initial improvements in terms of immediate visuo-spatial memory. After regression analyses, visuo-spatial improvement was found as a significant predictor of degree of eventual improvement	Traditional cognitive evaluations in rTMS trials are designed to provide a broad assessment of neuropsychological functioning across different cognitive domains	Cognition may have a relevant role as an early indicator of antidepressant response
Vanderhasselt et al. [39], 2009	15 TRD patients	A crossover placebo-controlled double-blind study	Patients underwent high-frequency (20 Hz) rTMS	DLPFC	Task-switching paradigm measuring auditory reaction time; initiation time; visual trials; movement time; visual trials	After 2 weeks of treatment	After 2 weeks of high-frequency rTMS, depressive symptoms improved in 53% of patients. After a single session, mood did not improve, but attentional control was increased solely within TRD patients	The stimulation could be only partially active, and the cognitive task that was used was not tested for validity/reliability. The use of drugs may have had impairing effects on the attentional task	Among responders, attentional control may play a relevant role in the progress of mood disorders
Fitzgerald et al. [40], 2009	27 TRD patients	2-arm randomized double-blind study	16 patients received high-frequency left-sided stimulation, 11 patients low-frequency rTMS 5 week/days/week	DLPFC	Visuospatial memory (BVRT); verbal memory (HVLT); verbal fluency (COWAT); digit span subtest (WAIS)	Baseline; week 3; end point (after 4 weeks of treatment)	Significant overall improvements were shown in immediate verbal memory and fluency independently from the type of rTMS received	The relatively small sample size did not allow the generalization of findings. A sham control group was not included. Most of the patients were taking antidepressants when evaluated	High-frequency left rTMS and low-frequency right rTMS appear to be equally efficacious in treating major depression
McLoughlin et al. [41], 2007	46 TRD patients	Randomized single-blind study	Patients were randomized to receive a 15-day course of rTMS or a course of ECT	Left DLPFC	Global cognitive functioning (CAMCOG, CAMDEX MMSE); immediate short-term memory, attention and working memory (forward and backward digit spans); retrograde autobiographical memory (AMI); motor and psychomotor speed (TMT A); processing speed (SDMT); visual motor coordination (GPT); frontal/executive function (TMT B)	Baseline; after 15 daily sessions; end point (after 6 months of treatment)	HDRS scores did not differ between groups at 6 months. There was no difference before or after treatment on global measures of cognition and in gain in quality-adjusted life-years for ECT and rTMS treated patients	The small sample size did not allow the generalization of findings. Also, this is only a randomized single-blind study, potentially biasing the blinding of the study design	There was no difference between patients treated with ECT or rTMS before or after treatment on the neuropsychological profiles

Table 2. (continued)

Study [Ref.], year	Sample characteristics	Study design	Procedure	Location of stimulation	Cognitive domains measured and outcome instruments	Cognitive assessments	Main findings	Limitations	Conclusions
Avery et al. [23], 2006	35 subjects were randomized to receive rTMS and 33 sham TMS	Randomized controlled study	Patients were randomized to receive 15 sessions of active or sham rTMS	Left DLPFC	Verbal learning (RAVLT); intelligence (WAIS-R); visual attention and task switching (TMT A and B); cognitive state (MMSE); verbal fluency (COWAT) (color Stroop test); attention and orientation (GOAT)	Screening/ baseline; end point (after 4 weeks of treatment)	The response and remission rates for the TMS group were significantly greater for those who were treated with rTMS than for the sham group. Depressive symptoms were significantly reduced over time in the TMS group compared with the sham group. Both treatment groups showed significant improvements in cognitive functioning at follow-up but no significant differences regarding any of the neuropsychological test measures between groups	The sample size is still relatively small to allow the generalization of findings. Patients who had a history of ECT nonresponse or had a strong suicidal ideation were excluded. Subjects were not blind to treatment allocation, potentially biasing the blinding of the study design. Also, raters were not asked to guess the treatment allocation. Finally, a flexible-dose study design could provide additional information	Both treatment groups (active or sham TMS) showed significant improvements in cognitive functioning over time
Rosa et al. [42], 2006	42 TRD unipolar nonpsychotic subjects	Randomized single-blind study	Patients were randomly assigned to receive either rTMS or ECT	Left DLPFC	Intelligence (WAIS-R); memory (WMS); everyday memory problems (RBMT)	Baseline; after 2 weeks; end point (after 4 weeks of treatment)	There was no difference in terms of antidepressant efficacy between patients treated with ECT and those treated with rTMS although response and remission rates were relatively low for both treatments. There was no significant difference in the neuropsychological test performance after these treatments	The small sample size did not allow the generalization of findings. Also, this is only a randomized single-blind study, potentially biasing the blinding of the study design	Both treatments were associated with a degree of improvement in patients with TRD
Schulze-Rauschenbach et al. [43], 2005	30 patients with nonpsychotic TRD	Randomized, controlled study comparing the neurocognitive effects of unilateral ECT and rTMS	Patients received 10 sessions of rTMS	Left DLPFC	Learning and anterograde memory function (AVLT, memory for persons test); retrograde memory function (AMI Retrograde AVLT, 4-card task from the RBMT); subjective memory function (SSMQ); cognitive state (MMSE); visual attention (TMT A and TMT B); intelligence (digit span task of WAIS-R); memory span (letter number span); word fluency (Leistungsprüfungsystem)	Pretreatment; posttreatment (8.8 days after rTMS or ECT)	Improvements in long-term memory recall and recognition were found in patients treated with rTMS. In the rTMS group, some objective memory measures and the subjective memory rating were found to improve together with the improvement in mood reaching normal performance levels	Treatments included either unilateral ECT or left PFC rTMS. The study lacked a sham-treated patient control group, and patients were not randomly assigned to treatments. The small sample size did not allow the generalization of these preliminary findings	In patients treated with rTMS, cognitive performance remained constant or improved, and memory complaints were reduced. rTMS has no adverse memory effects compared to ECT

Table 2. (continued)

Study [Ref.], year	Sample characteristics	Study design	Procedure	Location of stimulation	Cognitive domains measured and outcome instruments	Cognitive assessments	Main findings	Limitations	Conclusions
Jorge et al. [44], 2004	20 patients with poststroke depression	Randomized, parallel, double-blind study of active versus sham rTMS	Patients were randomly assigned to receive 10 sessions of active or sham left PFC rTMS	Left PFC (middle frontal gyrus)	IQs (Barona equations); frontal executive functioning (Stroop test, TMT A and TMT B); verbal fluency (COWAT); verbal and nonverbal learning, memory, recognition (RAVLT, BVRT); language assessment (BNT); language comprehension and repetition (token test, sentence repetition subtest of the MAE); visuospatial and visuoconstructive functions (block design subtest from the WAIS-III); unilateral visual neglect (line bisection test)	Baseline; end point (after 3 weeks)	A significant reduction of depressive symptoms was reported. There were no significant changes in cognitive functioning between the active and the sham stimulation groups	A mixed sample of TRD (both unipolar and bipolar depression with either ischemic lesions of the right hemisphere or deep subcortical lesions of the left hemisphere) patients was recruited. Also, the small sample size restricts the statistical power and increases the probability of a type II error	rTMS may be an effective and safe treatment for patients with TRD and stroke
Moser et al. [28], 2002	19 middle-aged and elderly TRD patients	Randomized controlled trial	Each patient received active (n = 9) or sham (n = 10) rTMS	Anterior middle frontal gyrus	Executive (TMT A, TMT B, Stroop test, WAIS-R, digit symbol); verbal fluency (COWAT); language (BNT, sentence repetition); memory (RAVLT, % of learned words recalled after delay); visuospatial (judgment of line orientation)	Baseline; after 5 sessions of active/sham stimulation	Patients in the active rTMS group improved significantly on a test of cognitive flexibility and conceptual tracking	The small sample size did not allow the generalization of data	rTMS targeted at the anterior portion of the left middle frontal gyrus may be associated with cognitive improvements as assessed by TMT B
Padberg et al. [25], 1999	18 TRD patients	Double-blind, placebo-controlled parallel study	Each patient received 5 days of rTMS treatments at 250 daily stimuli	Left DLPFC	Explicit verbal learning and the retrieval of verbal information from short-term memory (verbal learning task consisting of 3 learning trials and a consecutive delayed recall task after distraction)	Prior to rTMS day 0; end point (after the last rTMS treatment on day 5)	A mild significant reduction of depressive symptoms (19%) was found after slow rTMS. Specifically, improvements in verbal memory (verbal learning task) were reported	The effect was clinically marginal and not reflected by self-rating scores. The small sample size (preliminary data) did not allow to conclude whether slow or fast rTMS is superior or whether both frequencies are effective	Safety and tolerability of rTMS treatment was confirmed. The mild antidepressant effect of slow rTMS was shown

AMI = Autobiographical Memory Interview; AVLT = Auditory Verbal Learning Test; BNT = Boston Naming Test; BVMT = Brief Visuospatial Memory Test; BVRT = Benton Visual Retention Test; CAMCOG = Cambridge Cognitive Examination; CAMDEX = Cambridge Examination for Mental Disorders of the Elderly; COWAT = Controlled Oral Word Association Test; DLPFC = dorsolateral prefrontal cortex; GOAT = Galveston Orientation and Amnesia Test; GPT = Grooved Pegboard Test; HDRS = Hamilton Depression Rating Scale; HVLT = Hopkins Verbal Learning Test; IQs = premorbid intelligence quotients; MAE = Multilingual Aphasia Examination; MMSE = Mini-Mental State Examination; PFC = prefrontal cortex; RAVLT = Rey Auditory Verbal Learning Test; RBMT = Rivermead Behavioral Memory Test; SDMT = Symbol Digit Modalities Test; SSMQ = Squire Subjective Memory Questionnaire; TMT A = Trail Making Test A; TMT B = Trail Making Test B; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale - Revised; WMS = Wechsler Memory Scale.

Table 3. rTMS open-label studies investigating cognitive effects in TRD patients

Study [Ref.], Sample characteristics	Study design	Procedure	Location of stimulation	Cognitive domains measured and outcome instruments	Cognitive assessments	Main findings	Limitations	Conclusions	
Pallanti et al. [52], 2012	28 TRD outpatients	3-week open-label study	Low-frequency rTMS (1 Hz) was used	Right DLPFC	Visual short-term memory capacity and implicit visuospatial learning (Corsi block-tapping test); phonemic verbal fluency (phonemic fluency task)	Baseline; end point (after 3 weeks of rTMS).	Low-frequency rTMS appeared effective in 42.9% of depressive resistant subjects. A significant reduction of both HDRS and HARS total scores was reported. The performances in the Corsi test and phonemic verbal fluency were improved independently from depressive symptoms variation. At the end of the rTMS protocol, a significantly reduced left hemisphere resting motor threshold was registered	This is an open-label study, the results of which may be subject to several confounders	A significant reduction in left hemisphere resting motor threshold was found only in responders, while a trend for improvement in cognitive function was found independently from clinical response
Furtado et al. [53], 2012	46 TRD patients	6-week open-label study	MRI and neuropsychological evaluations prior to rTMS. rTMS was provided as 10-Hz left DLPFC stimulation to 21 patients or sequential bilateral DLPFC stimulation to 23 patients for up to 6 weeks	DLPFC	Premorbid intelligence (WTAR); visuospatial memory (BVM2-R); verbal learning (RAVLT); visual attention (TMT); intelligence (digit span task of WAIS-R); verbal fluency (COWAT, Stroop test)	Baseline	There was no difference in pre-treatment neurocognitive profiles and medial temporal lobe volumes between treatment responders and nonresponders. Smaller pre-treatment left hippocampus volume showed a trend towards predicting eventual subjective improvement in depressive symptomatology	The small sample size had presumably insufficient power to detect subtle differences between treatment responders and nonresponders. Also, the study did not include a control group for comparison	Some structural alterations may have some potential for predicting outcome to rTMS
Kedzior et al. [45], 2012	10 TRD patients compared with 8 healthy volunteers	Open-label study	Patients underwent forty 20-min sessions of fast-frequency (10 Hz) rTMS over 20 days	Left DLPFC	General cognitive functioning (RBANS)	Baseline; end point (after 20 days of rTMS)	After rTMS, patients performed significantly better on the concept-shift ability when compared with healthy volunteers. A significant improvement in immediate memory assessed by Repeatable Battery for the Assessment of Neuropsychological Status and reduction in depressive scores was also observed from baseline to the end of the study	The lack of a matched clinical group and healthy control group is a first limitation. Also, the improvement in cognitive functioning and reduction in severity of depression symptoms could be due to the combination of pharmacological treatment and rTMS rather than rTMS alone	rTMS was associated with an improvement in selective cognitive functions that is not explained by practice effects on tasks administered repeatedly

Table 3. (continued)

Study [Ref.], Sample characteristics	Study design	Procedure	Location of stimulation	Cognitive domains measured and outcome instruments	Cognitive assessments	Main findings	Limitations	Conclusions	
Holtzheimer et al. [46], 2010	14 TRD depressed patients	6-week open-label study	Patients underwent 15 rTMS sessions administered over 2 days	Left DLPFC	General cognitive functioning (RBANS)	Screening/baseline; after day 3; after week 3; end point (after week 6 of rTMS)	Neuropsychological function did not decline with treatment and showed improvement at week 6. Only 1 patient reported increased suicidal ideation, 2 participants failed to complete the full course of open-label accelerated TMS treatments, and 36% did not complete all study visits. Response rates after 3 and 6 weeks of rTMS treatments were 43, 36 and 36%, respectively whereas remission rates at the same time points were 29, 36 and 29%	The small sample size and the open-label nature of the study represent major limitations	After TMS treatments, depression and anxiety significantly decreased, and antidepressant improvements persisted 3 and 6 weeks later
Levkovitz et al. [54], 2009	65 medication-free depressive resistant patients	4-week open-label study	Patients underwent high-frequency (20 Hz) deep rTMS over the PFC	Deeper brain regions over the PFC	General memory and learning, working memory and executive function, visual memory, attention and reaction time, semantic/verbal memory, decision making and response control (CANTAB)	Baseline; after 2 weeks; end point (after 4 weeks of rTMS)	A greater improvement in HDRS scores was reported with the use of high stimulation intensity compared with the low stimulation intensity. Cognitive improvements were also found	This is the first preliminary study aimed to evaluate the potential of deep TMS in psychiatric patients. The open-label nature of the study should be interpreted as a major limitation	Deep TMS was reported to be safe and effective in reducing depression
Bloch et al. [47], 2008	9 TRD adolescents	Open-label pilot study	Patients received a 14-day course of rTMS	Left DLPFC	General memory and learning, working memory and executive function, visual memory, attention and reaction time, semantic/verbal memory, decision making and response control (CANTAB)	Baseline; during rTMS; end point (after 2 weeks of rTMS)	Lower levels of depression were reported in the sample by both the BDI and Child Depression Rating Scale measures. Improvements in reaction time (immediate and at 1 month) and planning (at 1 month) were found	The small sample size did not allow the generalization of findings. These preliminary findings lack a double-blind, controlled study design	rTMS could be a possible therapeutic option for adolescent depression
Mosimann et al. [48], 2004	24 TRD outpatients	Open-label study	Patients were randomized for sham or real stimulation and received 10 daily rTMS sessions (20 Hz, 2-s trains, 28-s intertrain intervals, 100% of motor threshold)	Left PFC	Global cognitive functioning (MMSE); verbal memory, e.g. learning, recall and recognition (VLT); frontal executive functions (Stroop test, TMT A, TMT B, WFT)	Baseline; end point (after 2 weeks of rTMS)	Depression ratings revealed significant antidepressant effects within 2 weeks in both sham and real stimulation groups; however, there were no differences between patients who received sham and those who received real stimulation	The small sample size and the short observation period are major limitations. A delayed antidepressant response to real rTMS in older patients might be a reason for lack of efficacy	Treatment with rTMS was safe and did not induce cognitive deterioration. No differences were observed between subjects who received sham and those who received real stimulation

Table 3. (continued)

Study [Ref.], Sample characteristics	Study design	Procedure	Location of stimulation	Cognitive domains measured and outcome instruments	Cognitive assessments	Main findings	Limitations	Conclusions
Fabre et al. [49], 2004	11 patients with late-onset resistant vascular depression	Open-label study (10 Hz) rTMS	Left PFC	Memory, a verbal learning task (Grober and Buschke, percentage of learned words recalled after delay); language (verbal fluency); executive ability (TMT A, TMT B); visuospatial skills (Hive Test); attention (digit span forward and backward); global cognitive functioning (MMSE)	Baseline; end point (after 2 weeks of rTMS)	Five patients were responders, a significant improvement in HDRS scores with an education of 11.4 points from baseline was observed. Antidepressant response was correlated to the relative degree of prefrontal atrophy. After 2 weeks, an improvement in verbal fluency and visuospatial memory was also reported	Subjects were free of antidepressants for at least 1 week (2 weeks for fluoxetine) before study entry, but most of them required low doses of benzodiazepines for anxiety	rTMS may represent a valid therapeutic option alternative to electroconvulsive therapy in TRD
Martis et al. [50], 2003	15 subjects with unipolar and bipolar TRD	1–4 week open-label study	Left PFC	Speed of information processing, simple and choice reaction time (Stroop test); speeded word retrieval, verbal fluency (letter); working memory (WAIS-III letter number span); anterograde memory for verbal and visual information (WMS-R visual reproduction, WMS-R logical memory); mental alternations (timed measure of mental control requiring the subject to recite an alternating letter number sequence); premorbid IQ (new adult reading test); speeded task to evaluate fine motor speed and dexterity (GP); subjective perception of attention, memory (Squire Test)	Baseline; end point (3 days after the last rTMS)	The absence of gross adverse cognitive changes was reported. A modest but significant improvement in performance was reported in the following cognitive domains: working memory, executive function, objective memory, fine motor speed domains	Both unipolar and bipolar subjects were recruited. The small sample sizes (this was a preliminary trial), the lack of a control group (e.g. sham group and/or healthy controls) and the susceptibility of some components of the neurocognitive battery demand caution in interpreting findings	No adverse neurocognitive changes emerged with rTMS. Significant improvements in executive functions could not be explained by improved mood
Triggs et al. [51], 1999	10 TRD patients	2-week open-label trial	Left PFC	Recent memory (RHVLT); auditory attention span (digit span subtest of the WAIS-R); verbal fluency (COWAT); confrontational word retrieval (Boston naming test)	Baseline; end point (after 2 weeks of rTMS)	The scores on the HDRS and BDI were reduced by 41 and 40%, respectively. Antidepressant improvement was still significant at 1 and 3 months later. Also, rTMS treatments were associated with significant reductions in motor evoked potential threshold in 90% of patients who remained off psychotropic medications	Considering the open-label nature of the study, the placebo effect cannot be excluded. Also, whether the same antidepressant and prolonged drugs that were ineffective pre-rTMS may have prolonged the response to rTMS treatment is unknown. The sample was too small to allow the generalization of findings	Prefrontal rTMS may modify brain activity inducing rapid and prolonged antidepressant improvements

BDI = Beck Depression Inventory; BVMT-R = Brief Visuospatial Memory Test – Revised; CANTAB = Cambridge Neuropsychological Test Automated Battery; COWAT = Controlled Oral Word Association Test; GP = Grooved Pegboard; HDRS = Hamilton Depression Rating Scale; HARS = Hamilton Anxiety Rating Scale; IQ = intellectual quotient; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PFC = prefrontal cortex; RAVLT = Rey Auditory Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RHVLT = Revised Hopkins Verbal Learning Test; TMT = Trail Making Test; TMT A = Trail Making Test – A; TMT B = Trail Making Test – B; VLT = verbal learning task; WAIS-R = Wechsler Adult Intelligence Scale – Revised; WFT = Word Fluency Test; WMS-R = Wechsler Memory Scale – Revised; WTAR = Wechsler Test of Adult Reading.

provements in the cognitive functioning which were associated with a general reduction in the severity of depressive symptoms following rTMS.

It has been hypothesized that rTMS reduced depressive symptoms subsequently to improving neurocognitive functioning, but it is also possible that rTMS may first improve neurocognitive performance and later indirectly depressive symptoms. Importantly, rTMS seems to act independently on both neurocognition and depressive symptoms, perhaps by activating/enhancing different neural pathways and brain regions [45].

Studies using rTMS in TRD subjects need to be considered in the light of the following limitations. First, we did not carry out a meta-analysis because data from most of the studies that were focused on the main topic did not permit it. Specifically, samples included different neurocognitive measurements and different outcomes, and they assessed patients at different time points. Also, some studies (even those conducted using a prospective follow-up design) included a small sample size, having presumably insufficient power to detect subtle differences between treatment responders and nonresponders and not allowing a generalization of the preliminary findings. Second, not all cognitive tasks that were used within the studies were tested for validity and reliability and, importantly, the use of some medications (e.g. antidepressant medications) may have had impairing effects on attentional tasks. Third, most of the specified studies lacked a sham-treated patient control group, included mixed (both unipolar and bipolar subjects were recruited) samples, were open-label/cross-sectional in nature or adopted only a randomized single-blind design potentially not allowing the exclusion of the placebo effect and biasing the blinding of the study design. Fourth, the application of different stimulation parameters (i.e. stimulation intensity, frequency and duration) and possible differences in targeting and positioning of the coil as well as the use of limited

neurocognitive measures need to be adequately considered when evaluating the overall efficacy of rTMS on TRD symptoms according to the selected studies. Lastly, some variables (not carefully investigated in most of the existing studies in the literature) may affect the individual response to noninvasive brain stimulation. It has been reported that the existence of BDNF gene polymorphism is associated with a reduced individual response to brain stimulation [61].

The state-dependent modulation of rTMS is an additional parameter that may potentially affect the individual antidepressant and neurocognitive effects of rTMS. Importantly, some specific techniques such as neuronavigation may improve the efficacy and reproducibility of the mentioned cognitive effects. Cognitive training and individually tailored therapies may enhance the neurocognitive effects of noninvasive brain stimulation [62].

Conclusion

rTMS is a noninvasive brain stimulation that may be considered a valuable and promising technique for cognitive enhancement in TRD. rTMS has been associated with significant improvement in some neurocognitive domains, and no serious adverse neurocognitive changes have been reported in most of the considered studies. However, the cognitive enhancing properties of rTMS in TRD have not been confirmed in all the selected studies; therefore, no conclusive evidence may be drawn about the efficacy of rTMS as a possible treatment option in reversing cognitive impairments in TRD.

Further additional prospective sham-controlled studies are required in order to carefully test the efficacy of rTMS to induce stable and long-term neurocognitive improvements.

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