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A meta-analysis of the effects of repetitive transcranial magnetic stimulation on aphasia rehabilitation in stroke patients

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Abstract

Background & Objective: Aphasia—acquired loss of the ability to understand or express language—is a common and debilitating neurological consequence of stroke. Evidence suggests that transcranial magnetic stimulation (TMS) can significantly improve language outcomes in patients with aphasia. Repetitive transcranial magnetic stimulation (rTMS) has been reported to improve naming in chronic stroke patients with nonfluent aphasia since 2005. *Methods:* We conducted a systematic review and meta-analyses of TMS treatment studies in patients with aphasia. Eight electronic databases (PubMed, Medline, Embase, Scopus, ScienceDirect, Cochrane Central Register of Controlled Trials, Journals@Ovid, and clinicaltrials.gov) were searched for articles. Relevant studies were further evaluated and studies that met inclusion criteria were reviewed. We included studies if were: randomized controlled blinded clinical trials, meta-analyses or crossover designs of rTMS alone or with speech therapy or any other therapy tested with rTMS. Standard mean difference (SMD) for changes in picture naming accuracy was estimated.
Results: The literature search yielded 423 studies. Fifty articles were further evaluated to be included. Eleven met all inclusion criteria and were chosen for review. Eleven eligible studies involving 301 stroke patients were identified in this meta-analysis. Further analyses demonstrated prominent effects for the naming subtest (SMD = 1.26, 95% CI = 0.80 to 1.71, P=0.01), with heterogeneity (I2 = 69.101%). The meta-analysis continued to show that there was a statistically significant effect of rTMS compared with sham rTMS on the severity of aphasia. None of the patients from the 11 included articles reported adverse effects from rTMS.
Conclusions: There are some strong studies evaluating the efficacy of rTMS in stroke patients but further research is required to fully establish the usefulness of this treatment. This meta-analysis indicates a clinically positive effect of rTMS with or without speech and language therapy (SLT) for patients with aphasia following stroke in overall language function and expressive language, including naming, repetition, writing, and comprehension. Low-frequency (1 Hz) rTMS over the unaffected hemisphere is effective and compatible with the concept of interhemispheric inhibition. Moreover, the treatment of 1 Hz rTMS for patients with aphasia after stroke was safe.

Keywords: rTMS, neurorehabilitation, meta-analysis, stroke, aphasia, language recovery

INTRODUCTION

In recent years, advances in cognitive neuroscience, neurorehabiltation research, and neuroimaging have led to dramatic advances in our understanding of how the brain reorganizes in the setting of stroke and other forms of focal brain injury. These discoveries have, in turn, paved the way for the use of noninvasive neuromodulation technologies, such as transcranial magnetic stimulation (TMS), which can potentially be employed to create focal,

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persistent neuroplastic changes in brain activity. Repetitive transcranial magnetic brain stimulation has been studied worldwide since 1985[1] as a potential treatment for some disorders associated with stroke. Noninvasive brain stimulation has been explored as a potential adjunctive treatment for a variety of post-stroke deficits, including aphasia, one of the most common and debilitating cognitive sequelae of stroke.

Stroke-related aphasia is one of the most common consequences of cerebrovascular diseases and occurs in one-third of acute or subacute stroke patients.[2] Aphasia can incapacitate all modes of human communication, including language production, language comprehension, reading, and writing. Aphasia is a frequent sequel of stroke with serious effects on the patient's autonomy and quality of life and requires speech and language therapy by which significant improvements of language and communication deficits can be achieved if administered intensively and for prolonged periods.[3,4] Approximately 21–38% of stroke patients experience aphasia in the acute phase and up to 12% have severe aphasia even 6 months after their stroke.[2,5] While spontaneous recovery after a stroke is common in first 3–6 months, aphasia persists beyond this period in many patients and can become a chronic disability.

Encouragingly, over the course of the last decade, a growing body of evidence has supported the use of noninvasive brain stimulation approaches to enhance long-term recovery in persons with aphasia.[6-9] TMS is a noninvasive procedure that uses magnetic fields to create electric currents in discrete brain areas.[10,11] TMS involves discharging a current through a coil of copper wire that is held over the subject's scalp. The current pulse flowing through the coil generates a rapidly fluctuating magnetic field that penetrates the scalp and skull unimpeded, and induces a changing electrical field in the cerebral cortex below the coil. The physiologic response appears to be caused by current flow in the cortical tissue, which leads to neuronal depolarization, exciting or inhibiting the cortex.[12] The participant feels a light tap on the scalp, may feel a twitch of the face muscles, and hears a brief, loud click as the current passing through the coil tightens the copper wire. Participants report that this is not unpleasant. The stimulation of the brain itself is painless. Depending on the stimulation parameters employed, TMS can be applied in ways that are understood to have either excitatory or inhibitory effects on underlying brain areas. The excitatory or inhibitory effects of TMS are dependent on the frequency at which it is administered; Repetitive TMS (rTMS) delivered at frequencies <5 Hz decreases excitability of affected cortical areas, while rTMS at higher frequencies increases excitability. When rTMS is applied as multiple stimuli (trains) of appropriate frequency, intensity, and duration, rTMS can lead to increases or decreases in excitability of the affected cortex that last beyond the duration of the train itself.[13] Slow rTMS, where 1 magnetic pulse is applied every second (1 Hz), delivered to the motor cortex can give rise to a lasting decrease in corticospinal excitability.[14,15] Mounting studies have demonstrated that inhibitory low frequency rTMS (≤1 Hz) over the unaffected hemisphere can improve language function in poststroke aphasic patients with left hemispheric lesions.[16-19] Conversely, fast rTMS (5, 10, or 20 Hz) can induce a transient increase in cortical excitability. The maximum output of a TMS device can reach up to 2.5T. To achieve focal brain stimulation, rTMS is often applied with a figure 8-shaped stimulation coil (7cm in diameter), where the area of the brain cortex affected is approximately 1cm, located in the center where the 2 wings of the figure 8-shaped coil meet.

Studies in patients with aphasia involving TMS have reported improvement in a variety of language functions, ranging from better accuracy in picture naming[6,8,20-22] to self-perceived improvement among patients in the ability to communicate[23,24] after TMS. This article presents an overview of repetitive transcranial magnetic stimulation (rTMS) where this new technology is explained in relationship to treatment of aphasia. The present systematic review and meta-analysis study aimed to investigate the efficacy of rTMS on aphasia rehabilitation in aphasic patients with stroke.

METHODS

One reviewer (MGH) carried out independent literature searches to identify potential treatment studies of rTMS in post-stroke aphasia. The following databases were used to conduct electronic searches to identify relevant studies: PubMed, Medline, Embase, Scopus, ScienceDirect, Cochrane Central Register of Controlled Trials, Journals@Ovid, and clinicaltrials.gov. The search terms were "aphasia OR language disorders OR anomia OR linguistic disorders AND stroke AND transcranial magnetic stimulation". The searches were limited to human studies written

in English and published between January 1960 and January 2020.

Table 1 provides detailed criteria for identifying studies for the meta-analyses. In keeping with the main objective of this review, we included all studies that carried out treatment using rTMS in stroke patients with aphasia, regardless of the trial (or experimental) design of the study. Studies that implemented between-subject or randomized controlled (RCT) design, cross-over trials, and within-subject or pre-post trials were all included. Since picture naming is one of the most frequently used batteries for assessing improvement in language abilities after treatment

Table 1: Inclusion/exclusion criteria for identifying treatment studies

	Inclusion criteria	Exclusion criteria
Patients	Studies that included adults diagnosed with aphasia due to stroke No restrictions were applied based on the: ~ type of stroke (ischemia or hemorrhagic), ~ recovery phases (acute, subacute and chronic), or ~ specific anatomical locations of lesions	Studies that included non-stroke patients (e.g., Alzheimer's disease, Parkinson's) or those patients who did not suffer from aphasia (e.g., hemiparesis) Non-human subjects
Treatment	Studies that included rTMS as treatment No restrictions on the site of stimulation were applied. No restrictions as to the specific brain stimulation paradigms were applied: ~ for TMS studies that applied repetitive TMS (low or high frequency) or theta burst stimulation (continuous or intermittent) were included. No restrictions on the duration or timing of SLT	Studies that included rTMS but not as a treatment: ~ if a study involved <3 stimulation sessions ~ if a study involved multiple stimulation sessions but not on the same cortical location Speech intervention studies such as melodic intonation therapies, but without rTMS
Outcomes	Studies that included picture naming accuracy (change or raw scores after treatment), as part of a comprehensive neuropsychological battery or as a separate test	Studies that did not include picture naming accuracy in any capacity
Trial designs	Between-subject or randomized controlled trials, cross-over trials, and within-subject or pre-post trial designs were included	Review articles and book chapters Case reports with <4 patients
Data reporting	Studies in which reporting of the data was conducive to analyzing treatment effects: ~ means, standard deviations (SD), standard errors (SE), mean difference, SD difference, SE difference, p-values, or individual patient data were used as required for effect size calculations	Studies in which adequate information was not provided and/or if the authors did not respond to our e-mails requesting more information
Publication types	Studies that were published: ~ in peer-reviewed journals ~ between January 1960 – January 2020	Duplicate articles Non English articles

with rTMS[25], we included studies that reported raw scores or changes in picture naming accuracy. Picture naming accuracy reflects the number of correctly articulated names of objects, displayed to patients as line drawings.[26] In cross-over trials, the same subjects undergo both the sham and the real treatment and changes in accuracy relative to baseline are compared between conditions. In incomplete crossover studies, a subset of subjects receives only real stimulation, while a subset receives sham stimulation first followed with real stimulation. The comparison is within-subject in the former subset (i.e., assessing post-stimulation performance relative to subject's baseline performance). The comparison in the latter subset is also within-subject but it is relative to subject's performance after the sham stimulation.

We placed no restrictions on stroke characteristics or types of aphasia in our inclusion criteria for treatment studies. We also did not restrict inclusion of studies based on brain stimulation parameters. Thus, studies that implemented rTMS of different kinds, including theta burst stimulation (TBS), were included. However, we excluded those studies in which: a) fewer than 3 stimulation sessions were administered per patient or b) stimulation was provided to different sites across sessions, because there is little evidence to suggest that single sessions or very few sessions of stimulation can translate to long-term benefits. In line with the notion that repeated sessions of stimulation are necessary to elicit therapeutic effects, most treatment studies have implemented protracted regimens involving 1–3 weeks of exposure to rTMS. Only those studies that administered rTMS in daily sessions (3–5 days/week) and kept the cortical target(s) constant throughout the treatment period were included. No restrictions were placed on the duration or time point of speech and language therapy (SLT) in these studies.

Studies that were published without English language translation were excluded. We also excluded publications of pilot studies where pilot data were also included in later publications, either with increased recruitment or extended follow-up evaluations. Our inclusion criteria permitted only those studies that provided treatment with either rTMS in ≥4 patients. In summary, the following inclusion criteria were applied in the evaluation of studies: 1) the patients were adults diagnosed with aphasia due to stroke; 2) the number of participants in the study was ≥4; 3) the outcome measures included picture naming accuracy before and after brain stimulation; and 4) the number of stimulation sessions was ≥3.

Data from each study were independently extracted by all authors using a standard data recording form that included the study design, number of subjects, mean age, stroke duration, treatment protocol (i.e., rTMS frequency, intensity, number of pulses, and additional interventions), dropout number, information regarding study quality, outcome measures, and pretreatment and post-treatment means and standard deviations for outcome measure. Various aphasia assessment outcome measures were used across the studies, some of which assessed multiple measures. For the purposes of this meta-analysis, the measure used to assess each study was the explicitly declared primary outcome. If the primary outcome was not clearly defined, the first outcome reported with a mean and SD in the results section was used. Comprehensive MetaAnalysis (CMA) Software version 3 (Biostat Inc., USA) was used to conduct this meta-analysis.

RESULTS

Characteristics of the included studies

We identified 423 unique records from the database searches. After screening the titles and abstracts, we excluded records and obtained the full texts of the remaining 29 articles. After further assessment, 11 studies[6,22,27-35] fulfilled the inclusion criteria (Figure 1). Some studies have been completed but have not been published, and some of them are ongoing, but we have been unable to obtain unpublished data. Eleven studies involving a total of 301 participants were included. All studies investigated the effect of rTMS versus sham rTMS (Table 2). Six trials explored the effect of rTMS combined with speech and language therapy. A total of 301 participants were randomized across eleven randomized comparisons that contrasted real rTMS with sham rTMS. The mean patient age reported in the eleven trials was 63.13 years. All participants suffered from ischemic infarct within the left or right middle cerebral artery territory. Some of patients were right-handed and some of them were left-handed.

Trials indicated the length of time elapsed since the participants had experienced the onset of their aphasia; the widest time range post-onset was 24 to 72 months.[15] The shortest mean length of time since the onset of the participants' aphasia was 28 days.

Using the 6-point Aphasia Severity Rating Scale (ASRS), the severity of aphasia was reported

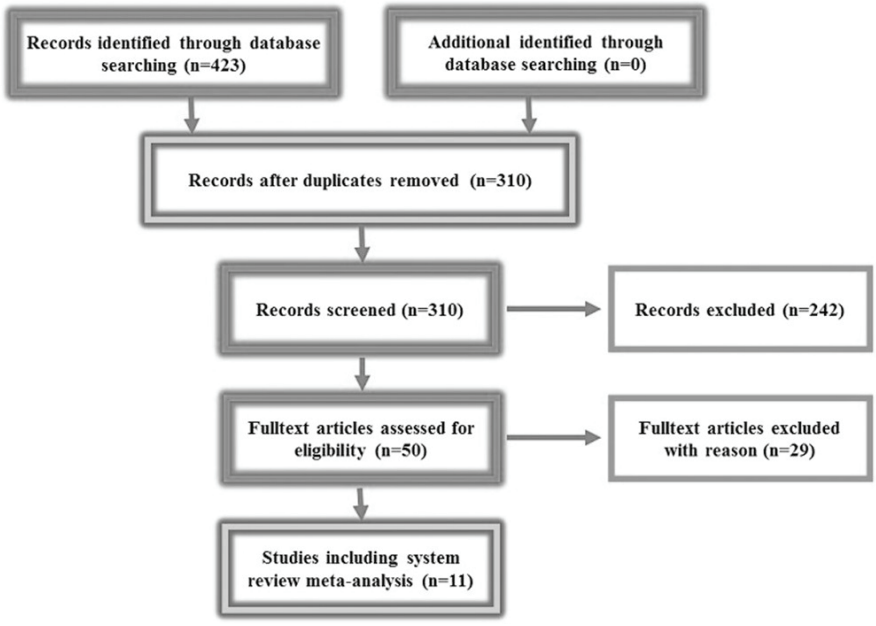

Figure 1. Flow chart for the inclusion of studies.

by 3 trials. The therapeutic procedures used in five trials consisted of rTMS sessions and specific language training. In these trials, immediately after finishing the rTMS treatment, both the experimental and control participants underwent speech and language therapy sessions for 45 minutes. The patients of the other study were only treated with real rTMS or sham rTMS sessions. In all trials, rTMS was performed with a Magstim Rapid stimulator (Magstim Company, Whitland, UK) equipped with an air-cooled figure-of-eight coil (each loop measured 70 mm in diameter). All trials used 1 Hz rTMS with an intensity equaling 90% of the daily defined individual resting motor threshold.

The treatment and sham stimulation sessions of eleven trials were conducted 20 min per day, for 10 days a 2-week period, whereas those of two trials were performed for a 3-week period. All included trials targeted the triangular part of the right inferior frontal gyrus (IFG). The sham stimulation condition of three studies was performed with an air-cooled sham coil that looks and sounds similar to the discharge of real TMS coil. The sham coil was placed at the same site on the scalp and with the same stimulation parameters used for the real rTMS procedure. The other eight studies used the same coil used the real rTMS placed over the vertex. All trials measured language outcomes. In those cases in which the data for this comparison were available, they are presented below in relation to the expressive language.

Primary outcomes Severity of aphasia impairment

All trials compared the active rTMS group with a group that received sham rTMS by measuring the severity of each participant's aphasia impairment. The language assessment batteries included the Aachen Aphasia Test (AAT) global scores and the Boston Diagnostic Aphasia Examination (BDAE). We obtained statistical summary data suitable for inclusion within a metaanalysis from these eleven trials.

The standardized mean difference (SMD) measure of effect is used when studies report efficacy in terms of a continuous measurement, such as a score on a pain-intensity rating scale. The SMD is also known as Cohen's d. The SMD is sometimes used interchangeably with the term "effect size." Generally, the comparator is a placebo, but a similar calculation can be used if the comparator is an alternative active treatment.

Pooling the available data using SMDs, we observed heterogeneity (I^2= 69.101 %, P= 0.001). The data were pooled using a fixed and random -effects model. There was a significant difference between the real rTMS groups and sham rTMS groups (SMD = 1.26, 95% CI = 0.80 to 1.71, P=0.01) (Figure 2). Sensitivity analyses were conducted after omitting Heiss WD's study, which has an unclear risk of allocation concealment bias and a high risk of incomplete outcome bias (SMD = 1.04, 95% CI = 0.52 to 1.56, P=0.01). The meta-analysis continued to show that there was a

Table 2: Characteristics of the included studies

Study	Participant	First language	Mean age	rTMS method	Coil position	Sham rTMS method
Barwood *et al*.[6]	12	English	63.9	Low-frequency (1 Hz) rTMS was applied for 20 min per day, for 10 days	figure-of-eight.	Low-frequency (1 Hz) rTMS was applied for 20 min per day, for 10 days
Barwood *et al*.[27]	12	English	63.9	Low-frequency (1 Hz) rTMS was applied for 20 min per day, for 10 days	figure-of-eight.	Low-frequency (1 Hz) rTMS was applied for 20 min per day, for 10 days
Barwood *et al*.[28]	12	English	63.9	Low-frequency (1 Hz) rTMS was applied for 20 min per day, for 10 days	figure-of-eight.	Low-frequency (1 Hz) rTMS was applied for 20 min per day, for 10 days
Thiel *et al*.[22]	24	German	70.5	1 Hz rTMS followed by 45 minutes of speech and language therapy.	figure-of-eight.	1 Hz rTMS followed by 45 minutes of speech and language therapy.
Seniów *et al*.[29]	40	Polish	60.7	1 Hz rTMS, immediately after each 30-minute rTMS session	figure-of-eight	1 Hz rTMS, immediately after each 30-minute rTMS session
Heiss *et al*.[30]	29	German	68.37	1 Hz rTMS followed by 45 minutes of speech and language therapy.	figure-of-eight	1 Hz rTMS followed by 45 minutes of speech and language therapy.
Hartmann *et al*.[31]	21	German	65	1 Hz rTMS with for 20 min, 10 sessions of rTMS over	figure-of-eight	1 Hz rTMS with for 20 min, 10 sessions of rTMS over
Waldowski *et al*.[32]	26	Polish	61.2	1-Hz rTMS was applied for 30 minutes.	figure-of-eight	1-Hz rTMS was applied for 30 minutes.
Heikkinen *et al*.[33]	17	Finnish	57	1-Hz rTMS 20min per day for 10 days	figure-of-eight	1-Hz rTMS 20min per day for 10 days
Ren *et al*.[34]	54	Chinese	60	1-Hz rTMS was applied for 30 minutes.	figure-of-eight	1-Hz rTMS was applied for 30 minutes.
Ren *et al*.[35]	54	Chinese	60	1-Hz rTMS was applied for 30 minutes.	figure-of-eight	1-Hz rTMS was applied for, 30 minutes.

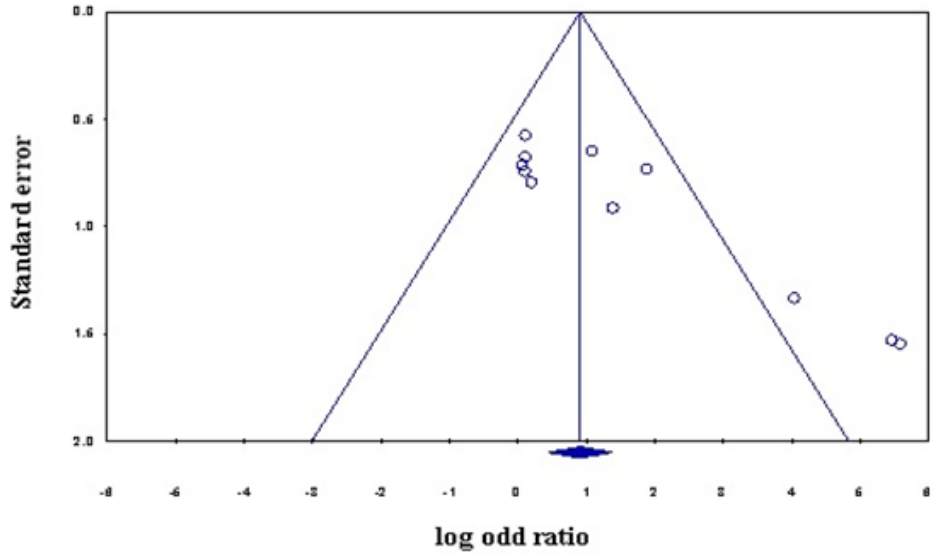

Figure 2. Forest plot of SMD and 95% CI for the severity of language impairment in patients.

statistically significant effect of rTMS compared with sham rTMS on the severity of aphasia.

Secondary outcomes

Adverse effects: None of the eleven trials reported any adverse effects.

Analysis for publication bias: As shown in the funnel plots in Figure 3, publication bias was observed for severity of naming, (Egger's test: P = 0.689 and Begg's test: P = 0.658). Figure 4 shows the meta-analysis of the eleven articles.

DISCUSSION

Summary of the main results

The present study supports the efficacy of using low-frequency rTMS in the right homologs of Broca's area on language recovery in aphasia patients with stroke. The statistical evidence was found for publication bias or heterogeneity, and

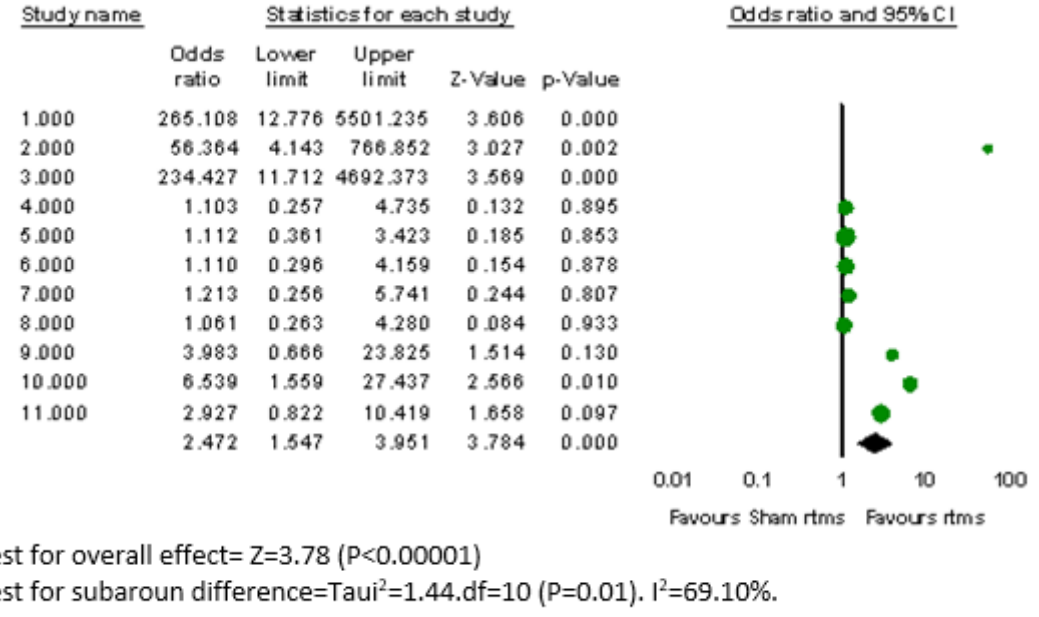

Figure 3. Funnel Plot of Standard Error by Log odds ratio.

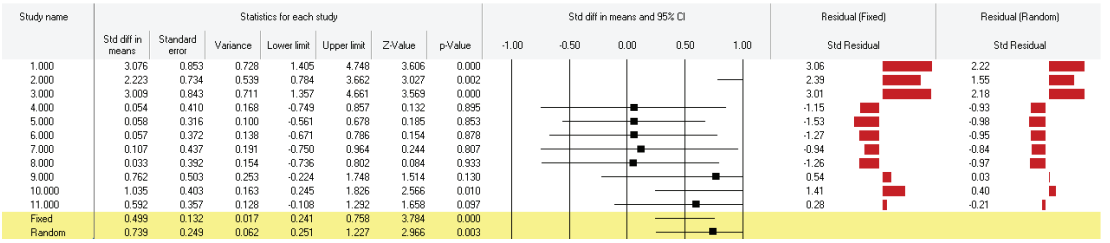

Figure 4. Meta-analysis of the eleven articles.

the results remained significant after any one of the trials was removed. The results of this meta-analysis suggest that significant differences between the groups' scores were evident in measures of language impairment, receptive language, and expressive language, all of which favored the use of low-frequency rTMS.

In the present meta-analysis, the significant mean effect size was 0.52 for naming, which indicate clinically significance. This result is also supported by some case reports and open protocol studies, which have indicated that significant improvements were obtained in naming or picture naming after applying 1 Hz rTMS over the right homologue of Broca's area.[21] An SMD of only 0.49 was obtained for the AAT and BDAE comprehension tests, which indicated that there was no statistically significant effect of real rTMS compared with sham rTMS on the outcome of those tests. Martin *et al*. showed that not all aphasic patients responded well, and that lesion site may play a role in each patient's response to TMS treatment.[36] Some enrolled clinical trials have established the underlying mechanism by which the application of rTMS to a homologous language region induces neural reorganization and reduces interhemispheric competition.[22,30,37] Consistent with these observations, studies 1, 2 and 3 showed that rTMS over the unaffected hemisphere has a positive effect on motor recovery by balancing of interhemispheric competition.[38]

The follow-up times differed in each trial, and only three trials reported the effect of rTMS follow-up times after treatment, which complicated further data analysis. Two trials followed up with patients 15 weeks after treatment, and one followed up with patients 2, 8, and 12 months after treatment. One 15-week follow up study revealed that severely aphasic rTMS patients demonstrated significantly greater improvements than those receiving repeated sham stimulation.[29] Another study showed that the rTMS subgroup with lesions that included the anterior part of the language area showed greater improvement primarily in naming reaction time 15 weeks after treatment.[32] Similar observations were reported by Barwood *et al*., who observed improved accuracy in naming on a number of subtests of the BDAE and Snodgrass & Vanderwart (1980) naming inventory up to 12 months after stimulation. These results suggest the long-term effects of follow-up on naming and repetition after rTMS treatment. Multicenter studies with large patient samples are needed to investigate the long-term effect of rTMS on aphasia.

The present meta-analysis is limited to low-frequency rTMS protocols and does not include other protocols, such as high frequency rTMS or patterned rTMS, theta burst stimulation (TBS). Some studies have showed that TBS over the right Broca's homologue improves naming performance in aphasic patients.[39,40] These studies were excluded as crossover trials or case reports. Still other studies confirmed that high-frequency rTMS over the left dorsolateral prefrontal cortex decreases vocal reaction times for picture naming in healthy individuals[41,42], increases the number of correct responses in patients with Alzheimer's disease[43,44], and facilitates action-naming performance in patients with progressive non-fluent aphasia.[45] However, the effect of high-frequency rTMS in stroke aphasia patients has not yet been studied in a randomized clinical trial.

Safety is an important consideration because rTMS can produce potential adverse effects, such as headaches and seizures. Thus, we investigated adverse effects in the present meta-analysis. No severe adverse effects were reported in the included studies. None of the patients reported that their language impairment worsened after treatment. This study suggests that rTMS is a safe treatment in the short term, but long-term follow-up is needed to further investigate the safety of this treatment. Although rTMS is generally assumed to be safe in patients following stroke, investigators should follow safety guidelines and examine the potential risk of post-stroke seizure related to rTMS.

Overall completeness and applicability of evidence

The results of this meta-analysis can be generalized for following conditions: (1) most patients are first-time stroke patients, (2) the majority of participants suffer from ischemic stroke, (3) nearly all participants are right-handed, and (4) 1 Hz rTMS with 90% RMT, targeting the triangular part of the right inferior frontal gyrus (IFG), is performed. Hence, the results may be of limited applicability for individuals with recurrent and hemorrhagic strokes and for left-handed patients. This meta-analysis also failed to subgroup the results by aphasic severity degree and aphasic syndrome.

The current meta-analysis provides sufficient evidence to draw conclusions about the benefits of low frequency rTMS in stroke aphasia. Low-frequency rTMS with a 90% resting motor threshold that targets the triangular part of the right inferior frontal gyrus (IFG) has a positive effect on language recovery in patients with aphasia following stroke. Further well designed studies with larger populations are required to ascertain the long-term effects of rTMS in aphasia treatment.

In conclusion, this meta-analysis indicates a clinically positive effect of rTMS with or without speech and language therapy (SLT) for patients with aphasia following stroke in overall language function and expressive language, including naming, repetition, writing, and comprehension. Low-frequency (1 Hz) rTMS over the unaffected hemisphere is effective and compatible with the concept of interhemispheric inhibition. Moreover, the treatment of 1 Hz rTMS for patients with aphasia after stroke was safe. No adverse effects were observed in patients in all eleven trials. However, further well-designed studies are necessary to determine the effect duration and long-term impact.

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DISCLOSURE

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REFERENCES

1. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985;1:1106-7.
2. Pedersen PM, Jorgensen HS, Nakayama H, *et al*. Aphasia in acute stroke: incidence, determinants, and recovery. *Ann Neurol* 1995;38(4):659-66.
3. Basso A. How intensive/prolonged should an intensive/prolonged treatment be? *Aphasiology* 2005;19:975-84.
4. Bhogal SK, Teasell R, Speechley M. Intensity of aphasia therapy, impact on recovery. *Stroke* 2003;34:987-93.
5. Wade DT, Hewer RL, David RM, *et al*. Aphasia after stroke: natural history and associated deficits. *J Neurol Neurosurg Psychiatry* 1986;49(1):11-6.
6. Barwood CHS, Murdoch BE, Riek S, *et al*. Long term language recovery subsequent to low frequency rTMS in chronic non-fluent aphasia. *NeuroRehabilitation* 2013;32(4):915-928.
7. Marangolo P, Fiori V, Di Paola M, *et al*. Differential involvement of the left frontal and temporal regions in verb naming: A tDCS treatment study. *Restor Neurol Neurosci* 2013:31(1):63-72.
8. Medina J, Norise C, Faseyitan O, Coslett HB, Turkeltaub PE, Hamilton RH. Finding the right words: Transcranial magnetic stimulation improves discourse productivity in non-fluent aphasia after stroke. *Aphasiology* 2012; 26(9):1153-68.
9. Shah-Basak PP, Norise C, Garcia G, Torres J, Faseyitan O, Hamilton RH. Individualized treatment with transcranial direct current stimulation in patients with chronic nonfluent aphasia due to stroke. *Front Hum Neurosci* 2015;9:201.
10. Pascual-Leone A, Davey N, Wasserman EM, Rothwell J, Puri B, eds: Handbook of transcranial magnetic stimulation. London: Arnold Pr; 2002.
11. Wasserman EM, Epstein CM, Ziemann U, Walsh V, Paus T, Lisanby SH, eds: The Oxford handbook of transcranial stimulation. New York: Oxford Univ Pr; 2008.
12. Rothwell JC. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J Neurosci Methods* 1997;74:113-22.
13. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998; 15:333-43.
14. Chen R, Classen J, Gerloff C, *et al*. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997;48:1398-403.
15. Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clin Neurophysiol* 2000;111:800-5.
16. Hu XY, Zhang T, Rajah GB, *et al*. Effects of different frequencies of repetitive transcranial magnetic stimulation in stroke patients with non-fluent aphasia: a randomized, sham controlled study. *Neurol Res* 2018; 80(6):859-65.
17. Zhang H, Chen Y, Huetal R. rTMS treatments combined with speech training for a conduction

aphasia patient: a case report with mri study. *Medicine* 2017; 96:32:7399.
18. Sebastianelli L, Versace V, Martignagoetal S. Low-frequency rTMS of the unaffected hemisphere in stroke patients: a systematic review. *Acta Neurol Scand* 2017:136(6):585–605.
19. Ilkhani M, Baghini HS, Kiamarzi G, Meysamie A, Ebrahimi P. The effect of low frequency repetitive transcranial magnetic stimulation (rTMS) on the treatment of aphasia caused by cerebrovascular accident (CVA). *Med J Islamic Repub Iran* 2017:31(1):137.
20. Baker JM, Rorden C, Fridriksson, J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke* 2010;41(6):1229-36.
21. Naeser M, Martin PI, Nicholas M, *et al*. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study. *Brain Lang* 2005; 93(1):95-105.
22. Thiel A, Hartmann A, Rubi-Fessen I, *et al*. Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. *Stroke* 2013;44(8):2240-6.
23. Rubi-Fessen I, Hartmann A, Huber W, *et al*. Add-on effects of rTMS on subacute aphasia therapy: Enhanced improvement of functional communication and basic linguistic skills. A randomized controlled study. *Arch Phys Med Rehabil* 2015; 96(11):1935-44. e2.
24. Szaflarski JP, Allendorfer JB, Banks C, Vannest J, Holland SK. Recovered vs. not-recovered from poststroke aphasia: The contributions from the dominant and non-dominant hemispheres. *Restor Neurol Neurosci* 2013; 31(4): 347-60.
25. Shah PP, Szaflarski JP, Allendorfer J, Hamilton RH. Induction of neuroplasticity and recovery in poststroke aphasia by non-invasive brain stimulation. *Front Hum Neurosci* 2013; 7:888.
26. DeLeon J, Gottesman RF, Kleinman JT, *et al*. Neural regions essential for distinct cognitive processes underlying picture naming. *Brain* 2007; 130(Pt 5):1408-22.
27. Barwood CH, Murdoch BE, Whelan BM, *et al*. Improved language performance subsequent to low-frequency rTMS in patients with chronic non-fluent aphasia post-stroke. *Eur J Neurol* 2011;8(7):935-43.
28. Barwood CH, Murdoch BE, Whelan BM, *et al*. The effects of low frequency Repetitive Transcranial Magnetic Stimulation (rTMS) and sham condition rTMS on behavioural language in chronic non-fluent aphasia: Short term outcomes. *NeuroRehabilitation* 2011;28(2):113-28.
29. Seniow J, Waldowski K, Lesniak M, *et al*. Transcranial magnetic stimulation combined with speech and language training in early aphasia rehabilitation: a randomized double-blind controlled pilot study. *Top Stroke Rehabil* 2013; 20:250-61.
30. Heiss WD, Hartmann A, Rubi-Fessen I, *et al*. Noninvasive brain stimulation for treatment of right- and left-handed poststroke aphasics. *Cerebrovasc Dis* 2013; 36:363-72.
31. Hartmann A, Rubi-Fessen I, Heiss WD. rTMS in the treatment of poststroke aphasia. *Clin Neurophysiol* 2013; 43:70-1.
32. Waldowski K, Seniow J, Lesniak M, Iwanski S, Czlonkowska A. Effect of low frequency repetitive transcranial magnetic stimulation on naming abilities in early-stroke aphasic patients: a prospective, randomized, double-blind sham controlled study. *ScientificWorldJournal* 2012:518568.
33. Heikkinen PH, Pulvermüller F, Mäkelä JP, *et al*. Combining rTMS With Intensive Language-Action Therapy in Chronic Aphasia: A Randomized Controlled Trial. *Front Neurosci* 2019;12:1036.
34. Ren C, Zhang G, Xu X, *et al*. The Effect of rTMS over the Different Targets on Language Recovery in Stroke Patients with Global Aphasia: A Randomized Sham-Controlled Study. *Biomed Res Int* 2019;2019:4589056.
35. Ren CL, Zhang GF, Xia N, *et al*. Effect of low-frequency rTMS on aphasia in stroke patients: a meta-analysis of randomized controlled trials. *PLoS One* 2014;9(7):e102557.
36. Martin PI, Naeser MA, Theoret H, *et al*. Transcranial magnetic stimulation as a complementary treatment for aphasia. *Semin Speech Lang* 2004;25(2):181-91.
37. Weiduschat N, Thiel A, Rubi-Fessen I, *et al*. Effects of repetitive transcranial magnetic stimulation in aphasic stroke: a randomized controlled pilot study. *Stroke* 2011; 42: 409-15.
38. Hsu WY, Cheng CH, Liao KK, *et al*. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke a meta-analysis. *Stroke* 2012;43:1849-57.
39. Kindler J, Schumacher R, Cazzoli D, *et al*. Theta burst stimulation over the right Broca's homologue induces improvement of naming in aphasic patients. *Stroke* 2012; 43: 2175-9.
40. VuksanovicJ, Jelic MB, Milanovic SD, *et al*. Improvement of language functions in a chronic non-fluent post-stroke aphasic patient following bilateral sequential theta burst magnetic stimulation. *Neurocase* 2015;21(2):244-50.
41. Cappa SF, Sandrini M, Rossini PM, *et al*. The role of the left frontal lobe in action naming: rTMS evidence. *Neurology* 2012; 59: 720-3.
42. Cotelli M, Manenti R, Rosini S, *et al*. Action and object naming in physiological aging: an rTMS study. *Front Aging Neurosci* 2010; 2: 151.
43. Cotelli M, Manenti R, Alberici A, *et al*. Prefrotal cortex rTMS enhances action naming in progressive non-fluent aphasia. *Eur J Neurol* 2012; 19:1404-12.
44. Cotelli M, Manenti R, Cappa SF, *et al*. Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer disease. *Arch Neurol* 2006;63: 1602-4.
45. Cotelli M, Manenti R, Cappa SF, *et al*. Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline. *Eur J Neuro* 2008;15: 1286-92.