Effect of Trans Cranial Magnetic Stimulation in Management of Dysphasia, A Systematic Review

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ABSTRACT

Background: Aphasia is the most disabling functional defect after ischemic stroke. It affects more than a third of all stroke victims. Effective therapeutic strategies are needed to treat aphasic patients. Novel techniques, such as methods of delivering cortical brain stimulation to modulate cortical excitability, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are just beginning to be explored. The purpose of repetitive transcranial magnetic stimulation (rTMS) application in the neuro-rehabilitation of aphasic patients is to act on specific networks involved in the pathophysiology of language processing and to promote adaptive cortical reorganization after stroke. TMS was shown to have lasting effects on cortical excitability that persisted beyond the actual stimulus delivery. Given the ability of this treatment to modulate cortical activity in a focal way, focus was soon placed on the use of this technique in various neurological and psychiatric diseases such as aphasia.

Aim of the work: The aim of this work is to evaluate the effect of Transcranial Magnetic Stimulation as a therapy for dysphasia in order to promote an evidence-based practice. This will be made by conducting a systematic review of literature in this topic area.

Materials and Methods: This was a systematic review. Seven electronic databases (Medline, Google scholar, CINHAL, Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and Embase) were searched for articles. Relevant studies were further evaluated and studies that met inclusion criteria were reviewed.

Results: The literature search yielded 5097 studies. Twenty-six articles were further evaluated to be included. Eleven studies met all inclusion criteria and were chosen for review. The studies provided moderate to strong evidence that rTMS may be an effective treatment for non-fluent stroke aphasia. We have found significantly higher scores on the language assessment scales of patients after the rTMS treatment than those with sham TMS treatment, in most of the included studies. The studies reviewed here established the beneficial effect of rTMS in multiple language domains. The domain of naming is the most affected, with almost all studies demonstrating improvement in naming after stimulation.

Conclusion: The current systematic review suggests that inhibitory low frequency rTMS with 90% resting motor threshold (rMT) targeting pars triangularis of the right inferior frontal gyrus can improve multiple language domains in right-handed post-ischemic stroke patients.

Keywords: Dysphasia, TMS, language assessment, treatment.

INTRODUCTION

Aphasia is the most disabling functional defect after ischemic stroke. It affects more than a third of all stroke victims. Effective therapeutic strategies are needed to treat aphasic patients, treatments, which can benefit people with aphasia include: intensive speech and language therapy (SLT), medications, stem cell transplantation and Transcranial Magnetic Stimulation. Novel techniques, such as methods of delivering cortical brain stimulation to modulate cortical excitability, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are just beginning to be explored (1). TMS was shown to have lasting effects on cortical excitability that persisted beyond the actual stimulus delivery (2). Given the ability of this treatment to modulate cortical activity in a focal way, focus was soon placed on the use of this technique in various neurological and psychiatric diseases such as aphasia (3).

Types of TMS, depending on the mode of stimulation, includes single or paired pulse TMS, Repetitive TMS (rTMS) {slow rTMS (1Hz) and fast rTMS (5, 10, or 20 Hz)} (3) and Intermittent Theta burst stimulation which is a patterned form of rTMS (4). The rationale of using inhibitory (1Hz) TMS as a complementary therapy in neuro-rehabilitation was mainly to decrease the cortical excitability in regions that are presumed to hinder optimal recovery (5).

Several studies used inhibitory rTMS over the right hemisphere homologue of the Broca area in the right inferior frontal gyrus (IFG) to facilitate naming and other language abilities in people with dysphasia (6). Many studies (7) support this approach by “interhemispheric inhibition hypothesis”. It assumes that damage to the left hemisphere releases the right hemisphere from transcallosal inhibitory input, resulting in increased right hemisphere activation and, consequently, increased behaviorally deleterious transcallosal inhibition of the already damaged left hemisphere (8).
There is a deficient good quality evidence for its role that support its use in a day to day practice. This study is an attempt to provide clinicians with such an evidence for an evidence-based practice of this technique.

METHODS

The systematic review was carried out according to the guidelines of the PRISMA protocol for systematic reviews and meta-analysis. It was registered in Prospero under protocol code CRD42017080098.

Search methods for identification of studies

Selection of studies: Two reviewer authors independently scanned the titles and abstracts of articles identified from electronic searches. The initial selection was wide-ranging to ensure that as many studies as possible are assessed as their significance to the review. The articles that is evidently irrelevant can be excluded in the early stages of the search (e.g. on the bases of titles and presented in electronic searches). Those that seemed eligible from their title or abstract were obtained in full text and underwent further inspection based on the eligibility criteria. Any discrepancy between the two authors were solved through discussion meetings, and a third author was consulted if necessary.

Eligibility Criteria (criteria for considering studies for this systematic review) were:

Study Design: We included all randomized controlled trials (RCTs) where rTMS was compared to sham or no TMS therapy.

We excluded review articles, case reports, case series, retrospective studies, uncontrolled studies and studies with less than 5 subjects.

Study Participants: We included all studies with patients diagnosed with any type of dysphasia, age above 18 years old, of either gender, regardless the duration, the severity and the lesion type or location.

We excluded studies that included non-stroke patients e.g. alzheimer, dementia and parkinson’s disease or those patients who had a stroke but didn’t suffer from dysphasia (only hemiplegia) and non-human subjects.

Intervention: We evaluated rTMS therapy, not tDCS or other modalities of transcranial stimulation.

We excluded studies that included rTMS but not as a treatment (studies performed on normal subjects) and studies applying less than 4 sessions of rTMS per patient because there was little evidence to suggest that single sessions or very few sessions of stimulation can translate to long-term benefits.

No restrictions on the site and dose of stimulation. We included studies where stimulation was provided to different sites across sessions (9).

We also had no restrictions to whether or not SLT was also administered in addition to rTMS therapy, its duration and timing. Most of studies provided SLT after completion of rTMS stimulation sessions. The noise produced by the rTMS device, to require the patients hold still during rTMS delivery and the produced facial muscle twitches are all obstacles to concurrent language therapy (9,10,11).

The control interventions were sham treatment or other conventional treatment (SLT) whether comparing “rTMS only” to “sham treatment”, or comparing “rTMS and SLT” to “sham treatment and SLT”.

Outcomes: We included studies using standardized language assessment measured before the start of treatment and after the end of treatment period and on scheduled follow ups (if any).

Studies evaluating other outcomes in addition to assessing language improvement were also included, however, only the language recovery outcomes were discussed and critically appraised in this work.

Search Strategy and search terms: To conduct electronic searches in order to identify relevant studies, we systematically searched the following databases: Medline, Google scholar, CINHAL, Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and Embase for published articles until December 2017 and we also searched the grey literature.

The search terms used included TMS or transcranial magnetic stimulation and a/dysphasia or management/treatment of a/dysphasia or effectiveness in a/dysphasia. Google scholar search limitations included the following to be excluded: - dementia/ -epilepsy/ -healthy/ -pain/ Alzheimer. No data limits were set for any of the other searches.

Data extraction and management in included studies: For each included study, two review authors independently extracted data of methods, participants, intervention, outcomes and
results. Again, disagreements were resolved through discussions.

Specifically, we extracted the following details: study design, random sequence generation, allocation concealment, blinding of participants and assessors, total number of participants, their gender, dropouts, their mean age and their handedness. In addition, first language, inclusion and exclusion criteria of participants, type of stroke, hemisphere localization of stroke, type of aphasia, mean time of onset post-stroke till the initial examination (pretreatment), dose of TMS, hemisphere target, no. of sessions, combined SLT, sham method, outcome measured and main results of the study.

RESULTS

Results of literature search:

Figure (1): Flow chart of excluded and included studies.

Bias Risk among the Studies: Two review authors independently assessed the methodological quality as described by the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Handbook). We created a risk of bias table and included a description and a judgment (low risk of bias, high risk of bias, or unclear risk of bias) for the following domains for each of the included studies:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
5. Incomplete outcome data.
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Table (1): Summary of study characteristics.

<table>
<thead>
<tr>
<th>No. of sessions</th>
<th>10 sessions once per day for 2 weeks except weekends.</th>
<th>10 sessions once per day for 2 weeks except weekends.</th>
<th>10 sessions (5 days/week)</th>
<th>10 sessions over twelve days once per day for 2 weeks</th>
<th>Received 10 sessions once per day for 2 weeks</th>
<th>15 sessions, 5 days week once per day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose of TMS, Hemisphere target</strong></td>
<td>Inhibitory low frequency 1 Hz rTMS for 20 min (1200 pulses) per session to the anatomic anterior portion of right BA 45 (pars triangularis). rTMS was applied at 90% of the rMT attained. Patient stimulation intensities ranged between 35-55% of maximum stimulator output.</td>
<td>Inhibitory 1 Hz rTMS with an intensity of 90% of rMT for 20 min over the triangular part of the right IFG (LIFG in Lt. handed).</td>
<td>Inhibitory 1 Hz rTMS with an intensity of 90% of rMT for 20 min over the unafflicted right Broca’s area with 1000 total pulses (500 pulses over pars triangularis followed by 500 pulses over pars opercularis) followed by 10 trains of 20 Hz stimulation, each lasting for 5 seconds with an intertrain interval of 30 seconds over the left Broca’s area of the affected hemisphere (5 trains over pars triangularis followed by 5 trains over pars opercularis).</td>
<td>1200 pulses of inhibitory 1 Hz rTMS at 90% of rMT for each session; the optimal site was in the right pars triangulars for 9 participants and was found to be in the right pars opercularis for 1 participant.</td>
<td>Inhibitory 1 Hz rTMS at 90% of the individual rMT for 20 min for each session over the right triangular part of the IFG (Brodmann area 45)</td>
<td>30 minutes sessions of inhibitory 1 Hz rTMS was applied at 90% of the rMT over the right-hemisphere homologue of Broca’s area (BA45) anterior portion (Rt. Pars triangularis). 1800 pulses delivered in a single train, with interstimulus interval = 2 second.</td>
</tr>
<tr>
<td><strong>Mean time of onset to assessment intervals post-stroke ± SD (E/C)</strong></td>
<td>(41.86 ± 15.24) 1/2 months (subacute)</td>
<td>(1.32 ± 0.60/ 1.67 ± 0.79) months (subacute)</td>
<td>(31.45 ± 1.02/ 1.0 ± 0.65) months (subacute)</td>
<td>(49.8 ± 29.6/58.6 ± 34.8) months (chronic)</td>
<td>(1.38 ± 0.71/ 1.67 ± 0.71) months (subacute)</td>
<td>(1.11 ± 0.88/ 1.32 ± 0.93) months (subacute)</td>
</tr>
<tr>
<td><strong>Type of aphasia</strong></td>
<td>Non-fluent / global (mild to severe)</td>
<td>Expressive (nonfluent aphasia) and Mixed (perceptive and nonfluent aphasia)</td>
<td>Non-fluent aphasia (mild to moderate)</td>
<td>Fluent and non-fluent (mild to severe)</td>
<td>Wernicke’s, Broca, mixed and Transcortical mixed</td>
<td></td>
</tr>
<tr>
<td><strong>Hemisphere localization of stroke</strong></td>
<td>Left hemisphere</td>
<td>Left hemisphere</td>
<td>Left hemisphere</td>
<td>Left hemisphere</td>
<td>Left hemisphere</td>
<td></td>
</tr>
<tr>
<td><strong>Type of stroke</strong></td>
<td>Cerebral infarction left middle cerebral artery (Lt. MCA)</td>
<td>Ischemic infarcts within MCA territory</td>
<td>Thromboembolic, non-hemorrhagic infarction in the distribution of MCA.</td>
<td>Ischemic stroke.</td>
<td>Ischemic stroke within the territory of MCA.</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age ± SD (E/C)</strong></td>
<td>(60.8 ± 5.98/ 67 ± 13.11) years</td>
<td>(61.0 ± 5.84/ 57.4 ± 9.6) years</td>
<td>(60.6 ± 7.1/ 62.6 ± 10.1) years</td>
<td>(67.9 ± 8.12/ 69.6 ± 6.67) years</td>
<td>(61.8 ± 11.8/ 59.7 ± 17) years</td>
<td></td>
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<tr>
<td><strong>Total no. (E/C)</strong></td>
<td>(49)</td>
<td>(49)</td>
<td>(51)</td>
<td>(55)</td>
<td>(55)</td>
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Note: 1. 10 minutes of inhibitory 1 Hz rTMS with an intensity of 90% of the daily-defined individual rMT over the Rt. IFG (PT) pars triangularis (Broca’s area homologue).
2. 1-Hz rTMS train consisting of 600 pulses, applied for 10 minutes of 90% of rMT over the contralesional pars triangularis (PT) within IFG.
3. 30 minutes (15 min. over PTr. and 15 min. over POp respectively) 1-Hz rTMS was applied at 90% of the rMT, stimulated two parts of Broca’s area homologues: the anterior part (PTr) and posterior part (POp) in order to minimize the inhibitory rTMS after-effect over the whole Rt. IFG.
4. 1200 pulses, suppressive 1 Hz, 90% of rMT for 20 minutes. TMS syn.: real 1Hz rTMS coupled with a synchronous picture naming training (online mode).
5. TMS sub.: real 1Hz rTMS followed by a picture naming activity (offline mode).
6. TMS sham.: sham 1Hz rTMS combined with a picture naming training (offline mode).
7. Over the Broca homologues (i.e. contralesional pars triangularis, PTr).
8. 10 daily sessions with a 20 minutes synchronous (concurrent) or subsequent (following) naming activity derived from the international Picture Naming Database.

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<table>
<thead>
<tr>
<th>Table (1): Continuation of summary of study characteristics.</th>
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<tbody>
<tr>
<td><strong>Main Results</strong></td>
</tr>
<tr>
<td>Right-handed patients treated with rTMS showed better recovery (There is significantly higher changes in global AAT test scores) of language function than sham-treated right-handers. Both left-handed patients also improved. All subtests contributed equally to the observed treatment effects with the largest difference observed in picture naming.</td>
</tr>
<tr>
<td>Language rating scores using: Aphasia Severity Rating Scale (ASRS), language scale of Hemispheric Stroke Scale (HSS) measured before the onset of treatment, after the end of last treatment session, 1 and 2 months after end of last treatment session.</td>
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<td>Real rTMS treatment resulted in a significant increase in multiple measures of discourse productivity compared to baseline performance, but no significant increase in other measures of fluency including: sentence productivity, grammatical accuracy and lexical selection.</td>
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<td>Higher gain in basic linguistic skills (AAT profile score, AAT subtests: Token test, Repetitions, Written language, Naming and Comprehension) as well as in functional communication (ANELT) were observed in the real stimulation group as opposed to the sham group.</td>
</tr>
<tr>
<td><strong>Outcome measured</strong></td>
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<tr>
<td>Changes in behavioural language functions assessed with rTMS treatment measured 1 week prestimulation (baseline) and at intervals 1 week, 2/months, 8 months, 12 months post stimulation (5 assessment sessions) assessed by naming performance, expressive language and auditory comprehension using the standard form of the boston naming test (BNT) and selected subtests of the boston diagnostic aphasia examination (BDAE).</td>
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<tr>
<td>The primary outcome measure, global AAT score absolute change, was significantly higher in the rTMS group compared with sham-treated patients. All subtests score in the rTMS group were higher after treatment and it was the highest for subset naming. There was no significant interaction between treatment and subset (A highly significant overall treatment effect was also found in the subset analysis). There were no differential treatment effects for different aphasia types. Inhibitory rTMS over posterior PFG is easy, safe and improves the effectiveness of conventional SLT.</td>
</tr>
<tr>
<td>The Aachen aphasia test (AAT) change = absolute difference between post-treatment and initial global score. The cookie theft picture description subtests of the Aphasia Severity Rating Scale (ASRS), language scale of Hemispheric Stroke Scale (HSS) measured before the onset of treatment, after the end of last treatment session, 1 and 2 months after end of last treatment session.</td>
</tr>
<tr>
<td>AAT including AAT profile score, Token test, Repetitions, Written language, Naming and Comprehension/ A scale of Amsterdam-Nijmegen Everyday Language Test (ANELT) / a naming screening Functional Independence Measure (FIM) comprehension and expression at baseline and after two week post treatment.</td>
</tr>
<tr>
<td><strong>Intergroup Comparisons</strong>: Both groups improved their naming abilities during 3 weeks of treatment significantly and continued to show improvement in the follow-up examination, yet there was no significant difference in average test scores between groups at any time. Significant decrease of naming RT as well as significant differences in ASRS ratings (as an indication of functional communication improvement) at follow up examination, 15-weeks after end of treatment, in the real group compared to sham group in patients with a lesion included or was located in the anterior (frontal) part of the language area.</td>
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<tr>
<td>There was an overall significant improvement shown by total AAT score, however in the subtests compared with sham group. The most prominent improvement was seen in the language, comprehension, and repetition domains. The experimental treatment was minimally effective for specific subgroups of pts: those with a frontal language area lesion (slightly better naming at follow up and better repetition at the post treatment assessment) and those with severe aphasia (slightly better naming at follow up and repetition at the post-treatment assessment; repetition become significant in experimental patients at the follow up examination 15 weeks after the end of treatment).</td>
</tr>
</tbody>
</table>

|---------|---------------------|-----------------|------------------|------------------|------------------------|------------------|

**Authors**

- **Third et al (16)**
- **Tsai et al (16)**
- **Waldowski et al (18)**
- **Wang et al (19)**
- **Weiduschat et al (20)**

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Characteristics of the included studies:

Study design:
The studies included in this review were randomized controlled trials (RCTs) published in peer-reviewed journals (5,6,9-17).

Characteristics of participants:

Sample size and age:
The 11 included trials involved 313 participants. Samples size ranged from 10 to 56 subjects. Weiduschat et al. (5) reported that they did not perform a sample size calculation because of the pilot nature of the study. All the other studies did not report any sample size calculation except the study by Thiel et al. (14). The mean ages of study subjects ranged from 59.7 to 71.2 years old.

Type/severity of aphasia:
Additionally, a range of aphasia severity and type had been included. Patients with both fluent and non-fluent aphasia, including Broca, Wernicke, Transcortical, Global and Amnestic were included in all studies with the exception of the studies by Medina et al. (6), Tsai et al. (15) and Wang et al. (17), which included patients with non-fluent types of aphasia only.

Characteristics of Intervention:

Hemispheric target:
Seven studies (5,12-15,17) targeted the inhibitory low-frequency (1 Hz) rTMS signals over the contralesional pars triangular was within the IFG (PTr) i.e. over the Broca’s area homologue. Heiss et al. (10) also targeted the the contralesional PTr which was the right PTr in all participants except the 2 left-handed patients where rTMS targeted the left PTr. While in the study by Medina et al. (6), the right PTr was targeted in 9 participants and the right pars orbitalis was targeted in 1 participant. The rTMS was applied with stimulation intensity of 90% of the rMT attained for each individual. Each session lasted for 30 minutes (15,16) or 20 minutes (5,12-17) or 10 minutes (20). Two studies (15,16) stimulated the right PTr for 15 minute and the right pars opercularis (POp) for another 15 minutes respectively. on the other hand, one study (13) used bihemispheric approach through sequential stimulation of each hemisphere; one continuous 1-Hz train at 110% of the rMT over the unaffected right Broca’s area with 1000 total pulses (500 pulses over pars triangularis followed by 500 pulses over pars opercularis). This was followed by 10 trains of 20-Hz stimulation, each lasting for 5 seconds with an intertrain interval of 30 seconds, over the left Broca’s area of the affected hemisphere (5 trains over PTr followed by 5 trains over POp).

Number of TMS sessions:
All studies applied the TMS for 10 sessions once per day for 2 weeks sparing weekends, except two studies (15,16) applied the TMS for 15 sessions, 5 days a week, once per day for 3 weeks.

Language Outcome(s) measured:
The outcome measures used in the recruited studies varies as different language assessment batteries were used across studies. Four of the studies (6,12,15,16) used the standard form of the BNT and selected subtests of the BDAE as an assessment of language functions. One study (16) also used the CPNT and ASRS of the BDAE. Four studies (5,10,13,14) used the AAT. One study (13) additionally used ANELT, a naming screening and FIM. Two (15,17) used the CCAT and PNT. Another study (13) used the ASRS and HSS.

Two studies (15,16) measured language functions at baseline, after 3 weeks (immediately post-treatment) and 15 weeks after the end of experimental treatment. Two other studies (15,17) evaluated language functions at baseline, on completion of stimulation after 2 weeks i.e. after 10th session (immediately post-treatment) and 3 months after the last intervention session. Two studies (5,13) did the assessment at baseline and after two-weeks (post-treatment). Only one study (12) did five assessment sessions; 1 week prestimulation (baseline) and at intervals 1 week, 2 months, 8 months and 12 months post stimulation. Another study (13) measured language rating scores before the onset of treatment (baseline), after the end of last treatment session, 1 and 2 months afterwards. One study (6) assessed language before intervention and 2 months after the completion of stimulation. Two studies (10,14) did not report when were the outcomes measured.

Main results:
All the studies were randomized and they all reported no significant group difference at baseline i.e. baseline comparability, except for the language measures (apart from AAT subtest written language) in the study by Rubi-Fessen et al. (13) where sham group was quantitatively slightly better; allowing for between group comparisons. Most of the included studies yielded significantly
better language outcomes in the group of patients treated with real TMS compared to the sham control group. In the study by Barwood et al., treatment-related changes were observed in the stimulation group, up to 12 months post-stimulation when compared to the placebo control group over time, for naming performance, expressive language and comprehension. For the majority of language subtests employed, significant differences in performance of the active cohort were identified between baseline and 8 months post-stimulation with subsequent performance plateaued at 12 months post-stimulation. For some subtests as naming actions, active group performance continued to improve from the 8 month to 12 month measures. In the study by Heiss et al., right-handed patients treated with rTMS showed significantly better language function recovery than sham-treated right-handers with the largest difference observed in picture naming. Both left-handed patients who received active rTMS treatment also improved. In the study by Khedr et al., shows significantly greater improvement in the language score measured after real rTMS compared with sham rTMS; this effect occurred immediately after the treatment session and remained significant for 2 months. In the study by Medina et al., real rTMS treatment resulted in a significant increase in multiple measures of discourse productivity compared to baseline performance, however there was no significant increase in other measures of fluency including: sentence productivity, grammatical accuracy and lexical selection. In the study by Rubi-Fessen et al., higher gain in basic linguistic skills as well as in functional communication were observed in the real stimulation group as opposed to the sham group. In the study by Thiel et al., the primary language outcome (global AAT score change) was significantly higher in the rTMS group compared with sham rTMS. Increase were largest for subtest naming and tended to be higher for comprehension, token test and writing. In the study by Tsai et al., real group showed significantly greater improvement over sham group in overall CCAT scoring and naming testing. Additionally, diabetes mellitus comorbidity yielded a lower language improvement and patients who had a lower contralesional rMT were predisposed to be a favourable therapeutic outcome, independent of aphasia type, severity and duration. In the study by Weiduschat et al., there was an overall significant improvement shown by total AAT score, but not the AAT subtests, when compared with sham group. In the study by Wang et al., TMSsyn group showed significantly superior results in CCAT, description and expression subtests, and action and object naming activity; the superior results lasted for 3 months; in comparison with rTMSsub and TMSsham groups.

On the other hand, two studies failed to demonstrate significance between group differences except for a certain group of patients. In the study by Seniów et al., although language functions improved in both groups, yet there were no significant differences in the degree of recovery. However, follow up 15 weeks after the end of treatment, revealed that severely aphasic rTMS patients demonstrated significantly greater improvement than patients receiving sham stimulation in repetition did. Similarly, in the study by Waldowski et al., although both groups significantly improved their naming abilities after treatment, no significant differences were noted between the 2 groups. Additionally, subgroup analysis, revealed that rTMS subgroup with a lesion including the anterior part of language area showed significantly greater improvement 15 weeks after treatment completion compared to sham group primarily in naming reaction time and also in functional communication abilities.

Table (3): Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors</th>
<th>Adequate sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Binding performance bias</th>
<th>Binding detection bias</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Free of selective reporting (reporting bias)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Barwood et al.</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Heiss et al.</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Khedr et al.</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Rubi-Fessen et al.</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>6</td>
<td>Seniów et al.</td>
<td>+</td>
<td>+</td>
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<td>7</td>
<td>Thiel et al.</td>
<td>?</td>
<td>?</td>
<td>+</td>
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<td>8</td>
<td>Tsai et al.</td>
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<td>+</td>
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<td>Waldowski et al.</td>
<td>+</td>
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<td>10</td>
<td>Wang et al.</td>
<td>?</td>
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<tr>
<td>11</td>
<td>Weiduschat et al.</td>
<td>+</td>
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DISCUSSION

In the recent years, there has been an increase in the number of research reports studying TMS in stroke patients.

This systematic review summarized the current RCTs investigating the efficacy of rTMS in the management of post-stroke aphasia. We found significantly higher scores on the language assessment scales of patients after the rTMS treatment than those with sham TMS treatment, in most of the included studies.

The studies reviewed here established the beneficial effect of rTMS in multiple language domains. The domain of naming is the most affected, with almost all studies demonstrating improvement in naming after stimulation. This could be attributed to being one of the most frequently used measures of language functions across the studies. Nevertheless, significant differences between the groups’ scores were also evident in different measures of language impairment, including receptive and expressive language. Some of the reviewed studies included both fluent and non-fluent aphasic patients, and they demonstrated improvements in expressive and receptive language as well (5,9,10,13-16), which could potentially indicate the efficacy of rTMS for both fluent and non-fluent aphasia. This result was also supported by some case reports (18) and pilot studies (19) which indicated that significant improvements were obtained in naming or picture naming after applying LF-rTMS over the right homologue of Broca’s area.

Our results were coherent with the concept that inhibitory rTMS to selected right hemisphere homologous language regions induced neural reorganization and reduced interhemispheric competition, as indicated by some enrolled studies (5,10,14).

In the study by Waldowski et al. (16) the authors reported only slight, non-significant difference between experimental and control group in the average test scores. The reason for this, as explained in one study (20) might be that the stimulation focused on both the PTr and POp rather than PTr alone. Two studies (15,17) found that the right POp plays a causal role in phonologic processing along with the ventral premotor cortex. POp permits enhanced modulation of the remaining bilateral dorsal language network through the arcuate fasciculus and mirror neuron system whereas the right PTr is truly harmful to the operation of the language circuits. Suppressing the right PTr might promote the function of the right POp through U fibers, which connect these 2 adjacent gyri, as was demonstrated in diffusion tension imaging tractography.

Effect of the lesion size/extent/type and severity of aphasia on patient response to rTMS:

Whereas all the included studies showed a significant improvement on aphasia after treatment, the studies by Seniów et al. (15) and Waldowski et al. (16) showed significant improvement only in specific conditions during follow up. The improvement in these 2 studies was seen in severely aphasic patients (15) or those with a lesion on the anterior portion of the language area (21). There was a mounting evidence that size and location of the stroke, as well as stroke type (haemorrhagic and ischemic infarction), and severity of aphasia may critically predict the magnitude of induced benefit from a particular stimulation paradigm (12).

Severe aphasic patients had a greater imbalance between these two hemispheres and can profit to a greater extent from contralesional inhibition (15).

Similarly, in the study by Jung et al. (21) the authors found that more severe aphasia and/or hemorrhagic strokes were associated with greater improvements in language deficits after tDCS treatment. Further research is needed to shed the light on the effect of rTMS based on these variables.

In the study by Khedr et al. (13), five cases in the real rTMS group showed no improvement in the language scores, three of them had extensive infarction (cortical and subcortical infarction) and 1 had cortical infarction (operculum). This might indicate that those patients with complete MCA
occlusion are not suitable to receive dual-hemisphere stimulation and perhaps would benefit more from high-frequency rTMS to the unaffected hemisphere to enhance activation of the right homologue of Boca’s area because the left Broca’s area is severely damaged. In one study (22) it was found that, after undergoing rTMS, one patient with chronic, nonfluent aphasia exhibited enhanced naming ability, while another did not. The reason for this difference according to the authors, was mainly because the latter patient had a lesion that extended into the IFG, including the left motor cortex, dorsal premotor cortex, the deep white matter adjacent to the left supplementary motor area and the posterior middle frontal gyrus, (which is an area that is vital for naming) (23). Consequently, structural integrity of the cerebral cortex is a prerequisite for efficacy. However, the interpretation from this study was limited by the lack of a control group and being inferred from results of only one subject.

**Relationship between time post-stroke and rTMS effectiveness:**

Given that the time post-stroke showed a wide variation across the included studies, and that these studies were able to demonstrate a similar degree of effectiveness, we concluded that rTMS appears to be effective in both subacute and chronic aphasia patients.

**Long term effects of rTMS in aphasia rehabilitation:**

One study (12) studied the long-term effect of rTMS. They showed that improvement of language continued even after 12 months post-therapy. A case exploration in the study by Martin et al. (22) combined behavioural and neurophysiological outcome measures to elucidate the effects of LF-rTMS for 10 days on two patients with chronic non-fluent aphasia and followed up the patients for 46 months post-TMS. One patient was identified as a ‘good responder’ and the other as a ‘poor responder’ to the TMS protocol. The good responding patient exhibited improvements in behavioural language outcomes that continued overtime. Further studies are needed to adequately assess the long-term effects of rTMS therapy in aphasic patients.

**Quality of the evidence:**

All the 11 included studies were randomized and sham-controlled, of which 6 clearly described random sequencing generation while the other 5 did not. Six trials also clearly described the method of allocation concealment while 5 did not. Blinding of personnel (participants, those performing SLT, and outcome assessors) was used in all trials. In 2 trials however, blinding of participants was not clearly mentioned. Unblinding of personnel performing the rTMS was inevitable. Incomplete outcome data who were more or less addressed adequately in 1 trial. The dropout rates in 4 studies were low and there were no withdrawals in 1 study. Three studies had a high (>20%) dropout rate without addressing it adequately, creating a potentially high risk of incomplete outcome data (attrition) bias. The remaining 2 studies were unclear about it, as they did not report losses or exclusions. All the studies, except one, did report all of the results, indicating a low risk of selective reporting bias (figure 2).

**Recommendations:**

**Language outcome measures:**

The use of the same language assessments at short intervals might facilitate practice effect and introduce a confounding factor (24).

In consideration of spontaneous recovery after stroke, long-term outcome measurement should be performed 3 months or longer after stroke (25).

More studies in the future should include fMRI to determine whether there are changes in cortical regions activation, to reinforce whether the hypothesized mode of action actually moderates the observed language improvement. Neuroimaging methods are also needed for precise localization of stimulation sites.

**CONCLUSION**

The current systematic review suggested that inhibitory low frequency rTMS with 90% rMT targeting pars triangularis of the right inferior frontal gyrus, can improve multiple language domains in right-handed post-ischemic stroke patients.

**REFERENCES**


