

## 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, CINAHL, 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 <sup>(1)</sup>. TMS was shown to have lasting effects on cortical excitability that persisted beyond the actual stimulus delivery <sup>(2)</sup>. 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 <sup>(1)</sup>.

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)} <sup>(3)</sup> and Intermittent Theta burst stimulation which is a patterned form of rTMS <sup>(4)</sup>. 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 <sup>(5)</sup>. 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 <sup>(6)</sup>. Many studies <sup>(7)</sup> 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 <sup>(8)</sup>.

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<sup>(9)</sup>.

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<sup>(9,10,11)</sup>.

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, CINAHL, 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.

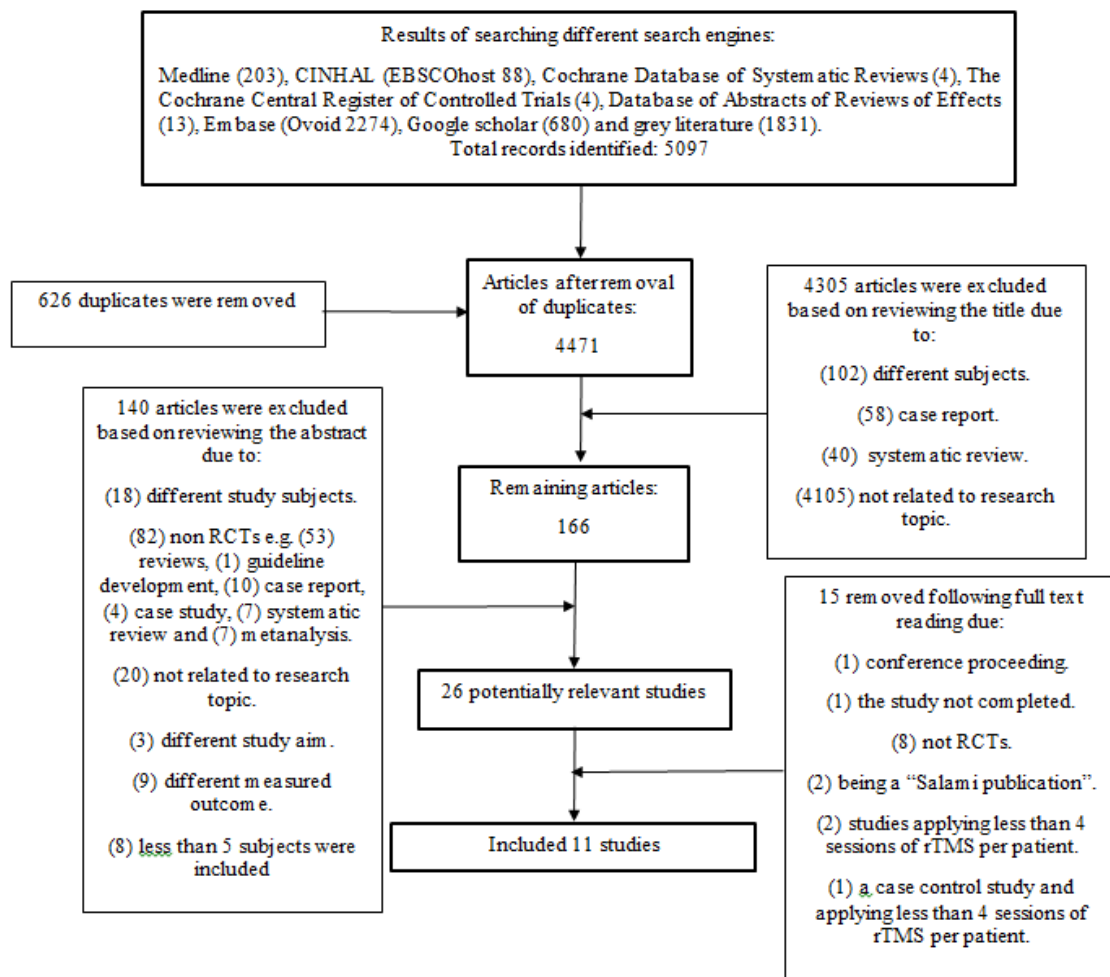
**Data extraction and management in included studies:** For each included study, two review authors independently extracted data of methods, participants, intervention, outcomes and

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. 4. Blinding of outcome assessment. 5. Incomplete outcome data. 6. Selective reporting.

**Table (1): Summary of study characteristics.**

No. of sessions	10 sessions once per day for 2 weeks except weekends.	10 sessions once per day for 2 weeks except weekends.	10 sessions (5 days/week)	10 sessions over twelve days once per day for 2 weeks	Received 10 sessions once per day for 2 weeks	15 sessions, 5 days a week once per day
<b>Dose of TMS, Hemisphere target</b>	Inhibitory low frequency, 1 Hz rTMS for 20 min (1200 pulse) per session to the apical anterior portion of right BA 45 (pars triangularis). Stimulation was applied at 90% of the rMT attained. Patient stimulation intensities ranged between 35–55% of maximum stimulator output.	Inhibitory 1 Hz of rTMS with an intensity of 90% rMT for 20 min over the triangular part of the Rt. IFG. (Lt. IFG in Lt. handed).	Bihemispheric approach: 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) 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).	1200 pulses of inhibitory 1Hz rTMS at 90% rMT for each session. the optimal site was in the right pars triangularis for 9 participants and was found to be in the right pars orbitalis for 1 participant.	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)	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= 1second.
<b>Mean time of onset to assessment intervals post-stroke ± SD (E/C)</b>	(41.88 ±15.24/41.52 ±18.36) months (chronic)	(1.32 ± 0.61/ 1.67 ± 0.79) months (subacute)	(31.45 ± 1.02/ 1.0 ± 0.65) months (subacute)	(49.8 + 29.6/ 58.6 + 34.8) months (chronic)	(1.38±0.71/1.62±0.71) months (subacute)	(1.11 ± 0.80/ 1.33± 0.96) months (subacute).
<b>Type of aphasia</b>	Non-fluent/ global (mild to severe).	Broca, Amnesic, Wernicke and Global.	Expressive (nonfluent aphasia) and Mixed (perceptive and nonfluent aphasia).	Non-fluent aphasia (mild to moderate)	Fluent and non-fluent (mild to severe)	Wernicke's, Broca, mixed and Transcortical mixed
<b>Hemisphere localization of stroke</b>	Left hemisphere	29 left 2 right hemisphere	Left hemisphere	Left hemisphere	Left hemisphere	Left hemisphere
<b>Type of stroke</b>	Cerebral infraction left middle cerebral artery (Lt. MCA)	Ischemic infarcts within MCA territory	Thromboembolic, non-haemorrhagic infarction in the distribution of MCA.	Ischemic stroke.	Ischemic stroke within the territory of MCA	Left ischemic
<b>Mean age ± SD (E/C)</b>	(60.8 ± 5.98/ 67 + 13.11) years	(68.5±8.19/ 69.0±6.33) years	(61.0 ± 9.8/ 57.4 ± 9.6) years	(60.6 ± 7.1/ 62.6 ± 10.1) years	(67.9 ± 8.12/ 69.60 ± 6.67)	(61.8 ± 11.8/ 59.7± 10.7)
<b>Total no. (E/C)</b>	(6/6)	(15/14)	(19 / 10)	(5/5)	(15/15)	(20/20)
<b>authors</b>	Barwood <i>et al</i> <sup>(12)</sup> .	Heiss <i>et al</i> <sup>(10)</sup> .	Khedr <i>et al</i> <sup>(9)</sup> .	Medina <i>et al</i> <sup>(6)</sup> .	Rubi-Fessen, <i>et al</i> <sup>(18)</sup> .	Seniów <i>et al</i> <sup>(11)</sup> .

10 sessions one/day.	10 sessions 1/day(5 days per week for 2 weeks)	15 sessions, 5 days a week, once per day for 3 weeks.	10 daily sessions with a 20 minutes synchronous (concurrent) or subsequent (following) naming activity derived from the international Picture Naming Database.	8–10 sessions once per day for 2 weeks period.
20 minutes of inhibitory 1 Hz rTMS with an intensity of 90% of the daily-defined individual rMT over the Rt. IFG (PTr) pars triangularis (Broca's area homologue).	1-Hz rTMS train consisting of 600 pulses, applied for 10 minutes of 90% of rMT over the contralesional pars triangularis (PTr) within IFG.	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.	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). TMS sub.: real 1Hz rTMS followed by a picture naming activity (offline mode). TMS sham.: sham 1Hz rTMS combined with a concurrent picture naming activity. Over the Broca homologue (i.e. contralesional pars triangularis, PTr).	Inhibitory 1-Hz rTMS for 20 minutes at 90% of the daily defined individual rMT over the Broca's area homologue (BA45) Rt. Pars Triangular (triangular part) of IFG.
(1.25 ± 0.61/ 1.68 ± 0.75) months (subacute).	(17.8 ± 7.2/18.3 ± 8.2) months (chronic)	(0.96 ± 0.64/ 1.61 ± 1.07) months (subacute)	TMS syn (16.8 ± 6.4) TMS sub (15.7 ± 8.5) TMS sham (16.1 ± 7.3) months (chronic)	(1.5/ 1.9) months (subacute).
Broca, Global, Amnesic and Wernicke (the most frequent).	Non-fluent (Broca, Transcortical motor and Global) mild to extremely severe (the majority were moderate and severe)	Broca, Wernicke, Mixed, Transcranial mixed.	Nonfluent aphasia (Broca, Transcortical-motor and Global aphasia with mild comprehensive deficits).	Broca, Wernicke (most common), Global and Amnesic.
Left hemisphere	Left hemisphere	Left hemisphere	Left hemisphere	Left hemisphere
Ischemic infarcts within the territory of MCA	Infarction Lt. MCA	Ischemic left MCA	Infarction	Ischemic or hemorrhagic stroke
(69.8 ± 7.96/ 71.2 ± 7.78) years	(62.3 ± 12.1/62.8 ± 14.5) years	(62.31 ± 11.03/ 60.05 ± 10.58) years	TMS syn (61.3±13.2) TMS sub (62.1±12.7) TMS sham (60.4±11.9) years	(66.6 / 63.75) years
(13/11)	(33/23)	(13/13)	(15/15/15)	(6/4)
Thiel <i>et al</i> <sup>(14)</sup> .	Tsai <i>et al</i> <sup>(15)</sup> .	Waldowski <i>et al</i> <sup>(16)</sup> .	Wang <i>et al</i> <sup>(17)</sup> .	Weiduschat <i>et al</i> <sup>(5)</sup> .

**Table (1):** Continuation of summary of study characteristics.

<b>Main Results</b>	Improved language performance over the 5 assessment points was identified for a range of expressive and receptive language behaviours when compared to placebo group	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.	Language rating scores using: 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.	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.	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.	Patient in both groups showed no significant differences in degree of recovery in all 3 assessed domains. The experimental treatment, however seems to be 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).
<b>Outcome measured</b>	Changes in behavioural language functions assessed with rTMS treatment measured 1 week prestimulation (baseline) and at intervals 1 week, 2months, 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).	The Aachen aphasia test (AAT) change = absolute difference between post-treatment and initial global score.	Language rating scores using: 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.	The cookie theft picture description subtests of the BDAE; 21 independent variables categorized into 4 aspects of speech fluency; discourse productivity, sentence productivity, grammatical accuracy and lexical selection, measured before intervention (baseline) and 2 months following the completion of stimulation	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.	3 main language functions of the BDAE, polish version (naming, repetition and comprehension) measured at baseline, immediately after 3 weeks of experimental treatment and 15 weeks after the conclusion of experimental treatment follow up.
<b>Authors</b>	<b>Barwood <i>et al</i></b> <sup>(12)</sup>	<b>Heiss <i>et al</i></b> <sup>(10)</sup>	<b>Khedr <i>et al</i></b> <sup>(13)</sup>	<b>Medina <i>et al</i></b> <sup>(6)</sup>	<b>Rubi-Fessen, <i>et al</i></b> <sup>(18)</sup>	<b>Seniów <i>et al</i></b> <sup>(15)</sup>

<b>Main Results</b>	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 subtest naming. There was no significant interaction between treatment and subtest (A highly significant overall treatment effect was also found in the subtest analysis). There were no differential treatment effects for different aphasia types. Inhibitory rTMS over posterior IFG is easy, safe and improves the effectiveness of conventional SLT	Real group showed significant improvement over sham group in overall CCAT scoring and the 4 evaluated CCAT subcategories. Within the real group significant differences were found in overall CCAT scoring, conversation, description, expression and repetition relative to pretreatment measurements. Real group also manifested higher object naming accuracy, action naming accuracy, shorter object naming RT and action naming RT than sham group and in comparison with its own baseline levels. At 3 months post-intervention, real group continued to show statistical differences in overall CCAT scoring, description, expression and repetition subscales relative to their baseline data. DM comorbidity yielded a negative impact (lower) on CCAT improvement. There was a negative correlation between contralesional (Rt.) rMTS and improvement in action naming accuracy after rTMS.	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.	Intergroup Comparison: TMSsyn exhibited significant improvement on all measures at post1 as well as total CCAT score, Expression, action and object naming accuracy at post 2. TMSsub showed significant improvement in CCAT score both at post 1 and post 2 and Conversation at post 1. TMSsham demonstrated improvement (with only borderline significance) in action-naming accuracy at post 1 and object naming accuracy at post 2 but not in CCAT score or subtests. There are significant intergroup differences with TMSsyn, exhibiting the most prominent improvement in the CCAT score, Description and Expression relative to TMSsub and Conversation, Description and Expression relative to TMSsham. TMSsyn group showed significantly superior improvement in object and action naming ability compared with rTMSsub and TMSsham at post1 and at post 2.	There was an overall significant improvement shown by total AAT score, but not in the subtests compared with sham group. Significant clinical improvements in the total AAT score in the therapy group, whereas the patients of the sham group did not improve significantly, looking at the AAT subtests, a significant improvement in the naming subtests in the TMS group was found. However, no significant group difference concerning improvements in single subtests.
<b>Outcome measured</b>	Absolute changes in global AAT score (however when it was measured was not reported).	The Picture Naming Test and (PNT) which involves both object and action naming accuracy and reaction time (RT) and the Concise Chinese Aphasia Test (CCAT) were 4 categories (conversation, description, expression and repetition) were evaluated, measured shortly before the 1 <sup>st</sup> session of intervention (baseline), on the day after 10 <sup>th</sup> session (post1) and 3 months after the last intervention session (post2).	Computerized Picture Naming Test (CPNT); accuracy of naming and reaction time (RT) and Aphasia Severity Rating Scale(ASRS) of the BDAE assessed 3 times [ at baseline (1-2 days before study), immediately after 3 weeks of experimental treatment and again 15 weeks after the end of the therapy (Follow up)].	Naming accuracy rate (object naming and action naming) and Concise Chinese Aphasia test (CCAT) total score in addition to 3 subcategories related to language production were assessed [(conversation, picture Description and naming objects and their use (Expression)] measured before treatment (baseline), after completion of treatment i.e. on the day of 10 <sup>th</sup> session (post 1) and 3 months after the intervention (post 2).	The German version of the AAT total score and subtests measured before (baseline) and 2weeks after (follow up) the period rehabilitation.
<b>Authors</b>	<b>Thiel <i>et al</i></b> <sup>(14)</sup>	<b>Tsai <i>et al</i></b> <sup>(15)</sup>	<b>Waldowski <i>et al</i></b> <sup>(16)</sup>	<b>Wang <i>et al</i></b> <sup>(17)</sup>	<b>Weiduschat <i>et al</i></b> <sup>(5)</sup>

**Characteristics of the included studies:****Study design:**

The studies included in this review were randomized controlled trials (RCTs) published in peer-reviewed journals <sup>(5,6,9-17)</sup>.

**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.* <sup>(5)</sup> 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.* <sup>(14)</sup>. 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 Amnesic were included in all studies with the exception of the studies by *Medina et al.* <sup>(6)</sup>, *Tsai et al.* <sup>(15)</sup> and *Wang et al.* <sup>(17)</sup>, which included patients with non-fluent types of aphasia only.

**Characteristics of Intervention:****Hemispheric target:**

Seven studies <sup>(5,12-15,17)</sup> targeted the inhibitory low-frequency (1 Hz) rTMS signals over the contralesional pars triangularis within the IFG (PTr) i.e. over the Broca's area homologue. Heiss et al. <sup>(10)</sup> also targeted 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. <sup>(6)</sup>, the right PTr was targeted in 9 participants and the right pars opercularis 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 <sup>(15,16)</sup> or 20 minutes <sup>(5,12-17)</sup> or 10 minutes <sup>(20)</sup>. Two studies <sup>(15,16)</sup> stimulated the right PTr for 15 minutes and the right pars opercularis (POp) for another 15 minutes respectively. On the other hand, one study <sup>(13)</sup> used a 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 <sup>(15,16)</sup> 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 <sup>(6,12,15,16)</sup> used the standard form of the BNT and selected subtests of the BDAE as an assessment of language functions. One study <sup>(16)</sup> also used the CPNT and ASRS of the BDAE. Four studies <sup>(5,10,13,14)</sup> used The AAT. One study <sup>(13)</sup> additionally used ANELT, a naming screening and FIM. Two <sup>(15,17)</sup> used the CCAT and PNT. Another study <sup>(13)</sup> used the ASRS and HSS.

Two studies <sup>(15,16)</sup> measured language functions at baseline, after 3 weeks (immediately post-treatment) and 15 weeks after the end of experimental treatment. Two other studies <sup>(15,17)</sup> 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 <sup>(5,13)</sup> did the assessment at baseline and after two-weeks (post-treatment). Only one study <sup>(12)</sup> did five assessment sessions; 1 week prestimulation (baseline) and at intervals 1 week, 2 months, 8 months and 12 months post stimulation. Another study <sup>(13)</sup> measured language rating scores before the onset of treatment (baseline), after the end of last treatment session, 1 and 2 months afterwards. One study <sup>(6)</sup> assessed language before intervention and 2 months after the completion of stimulation. Two studies <sup>(10,14)</sup> 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. <sup>(13)</sup> where sham group was quantitatively slightly better; allowing for between group comparisons. Most of the included studies yielded significantly

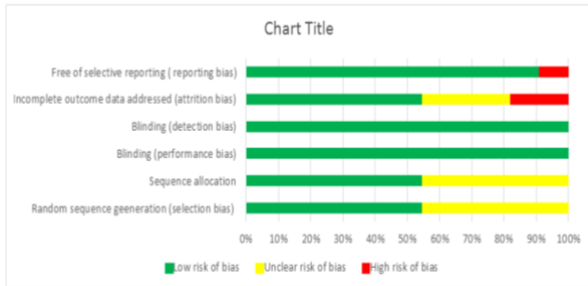
better language outcomes in the group of patients treated with real TMS compared to the sham control group. In the study by *Barwood et al.* <sup>(12)</sup> treatment-related changes were observed in the stimulation group, up to 12 months post-stimulation when compared to the placebo control group over 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.* <sup>(10)</sup>, 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.* <sup>(13)</sup>, 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.* <sup>(6)</sup>, 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.* <sup>(13)</sup> 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.* <sup>(14)</sup>, the primary language outcome (global AAT score change) was significantly higher in the rTMS group compared with sham-treated patients. Increase were largest for subtest naming and tended to be higher for comprehension, token test and writing. In the study by *Tsai et al.* <sup>(15)</sup>, real group showed significantly greater improvement over sham group in overall CCAT scoring and its 4 evaluated subcategories. Real group also manifested higher object and action naming accuracy and shorter object and action naming reaction time than sham group. At 3 months post-intervention, real group continued to show statistical differences 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.* <sup>(5)</sup>, 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.* <sup>(17)</sup>, 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 <sup>(15,16)</sup> failed to demonstrate significance between group differences except for a certain group of patients. In the study by *Seniów et al.* <sup>(15)</sup>, 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.* <sup>(16)</sup>, 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.

No.	Authors	Adequate sequence generation (selection bias)	Allocation concealments (selection bias)	Blinding (performance bias)	Blinding (detection bias)	Incomplete outcome data addressed (attrition bias)	Free of selective reporting (reporting bias)
1	Barwood et al., <sup>(12)</sup>	+	?	+	+	?	+
2	Heiss et al., <sup>(10)</sup>	?	?	+	+	-	+
3	Khedr et al., <sup>(13)</sup>	?	+	+	+	+	+
4	Medina, <sup>(6)</sup>	?	?	+	+	?	+
5	Rubi-Fessen et al., <sup>(13)</sup>	+	+	+	+	+	+
6	Seniów et al., <sup>(15)</sup>	+	+	+	+	+	+
7	Thiel et al., <sup>(14)</sup>	?	?	+	+	-	+
8	Tsai et al., <sup>(15)</sup>	+	+	+	+	+	+
9	Waldowski et al., <sup>(16)</sup>	+	?	+	+	+	+
10	Wang et al., <sup>(17)</sup>	?	+	+	+	+	-
11	Weiduschat et al., <sup>(5)</sup>	+	+	+	+	-	+



**Figure (2):** Risk of bias graph; review authors' judgements about each risk of bias item presented as percentages across all included studies.

## 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 language 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 tensor 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 Broca's area because the left Broca's area is severely damaged. In one study <sup>(22)</sup> 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) <sup>(23)</sup>. 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 <sup>(12)</sup> 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.* <sup>(22)</sup> 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 <sup>(24)</sup>.

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

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.

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