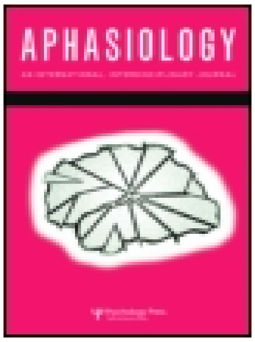

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Evaluating the quality of conduct of systematic reviews on the application of transcranial magnetic stimulation (TMS) for aphasia rehabilitation post-stroke

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ARTICLE

Evaluating the quality of conduct of systematic reviews on the application of transcranial magnetic stimulation (TMS) for aphasia rehabilitation post-stroke

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ABSTRACT

Background: Noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) are used to facilitate the recovery of language in stroke patients with aphasia. Although rTMS is a promising therapeutic method, further investigations are needed to expand the knowledge base about the use of the technique in stroke-induced aphasia.
Aims: To evaluate the quality of conduct of systematic reviews of randomized controlled trials (RCTs) of interventions on the application of rTMS for aphasia rehabilitation post-stroke using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) instrument.
Methods & Procedures: A search was performed of databases specific to systematic reviews. Four systematic reviews met the inclusion criteria. All aspects regarding the conduct of each individual systematic review was critically appraised using the AMSTAR 2 instrument.
Outcomes & Results: The overall confidence ratings based on weaknesses in critical domains identified by the AMSTAR 2 was low for one systematic review and critically low for the remaining three.
Conclusions: The quality of conduct of published systematic reviews of RCTs on the application of rTMS for aphasia rehabilitation post-stroke is low. The evidence for the effectiveness of rTMS on language recovery post-stroke remains inconclusive. The findings underscore the need for methodologically rigor trials on the applicability of TMS as an intervention approach for aphasia. Published guidelines to provide reliable and replicable results are urgently needed.

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Non-invasive brain stimulation (NIBS); RCTs; scientific rigour

Introduction

Aphasia, an acquired communication disorder, afflicts more than one-third of all stroke survivors (Heiss & Thiel, 2016). To date, there are no treatments enabling reparation of the brain damage (Di Pino et al., 2014). Pharmacological treatments for common aphasia symptoms (e.g., anomia) have been trialled, but no medication has yet been approved (see Saxena & Hillis, 2017 and references within). Traditional speech and language therapy (SLT) methods robustly remain the gold standard for aphasia rehabilitation (Breitenstein et al., 2017). Intensive and targeted SLT intervention improves language

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abilities for all aphasia types irrespective of time post-onset and aphasia severity (Saxena & Hillis, 2017). Nevertheless, there is an urgent need for further research to establish the best treatment approach or type of therapy, in relation to three key treatment components (Brady, Kelly, Godwin, Enderby, & Campbell, 2016): frequency (how often), duration (how long for) and dosage (how much).

In recent years, brain stimulation techniques have also been applied to stroke patients with aphasia to facilitate language recovery. Transcranial magnetic stimulation (TMS) is one type of noninvasive brain stimulation (NIBS) technique used in the evolving field of neurostimulation protocols for stroke rehabilitation (Cappa, 2011). Variations in TMS methods with regard to intensity, frequency and duration of the stimulation can yield temporary decreases or increases in the excitability of the affected brain area. For post-stroke aphasia rehabilitation, repetitive TMS (rTMS) protocols have been explored for their potential to induce changes in brain activity that last beyond the period of stimulation. Such effects could reflect basic synaptic mechanisms, such as long-term potentiation (LTP) (i.e., persistent strengthening of synapses) and/or long-term depression (LTD) (i.e., long-lasting decrease in synaptic strength) plasticity (Huang et al., 2017). In general terms, excitatory (high-frequency, 5–20 Hz) rTMS increases cortical excitability, whereas inhibitory (low-frequency, below 5 Hz) rTMS suppresses brain activity.

New research has revealed that applying excitatory rTMS over the lesioned left hemisphere improves language functions in individuals with post-stroke aphasia. Szaflarski et al. (2011) applied fMRI guided excitatory theta burst stimulation[1] (TBS) to residual Broca's area of the left hemisphere in eight patients with chronic or moderate aphasia and found significant improvements in semantic fluency ($p = .028$), and an overall trend towards improvement in communication ($p = .075$) which were associated with stronger language lateralization to the left (dominant) hemisphere. This last finding was supported by another excitatory (to the left hemisphere) TBS study (Griffis, Nenert, Allendorfer, & Szaflarski, 2016). Also, Vuksanovic et al. (2015) applied inhibitory TBS over the right Broca's homologue and immediately after excitatory TBS over the left Broca's area. The authors reported improvement in several linguistic domains, most notably in propositional speech, semantic fluency, and for cognitive skills such as short-term verbal memory, and verbal learning.

However, the rTMS protocol that has been examined the most and has demonstrated good potential for post-stroke aphasia recovery is inhibitory rTMS over the homologue frontal language areas in the right hemisphere (e.g., Abo et al., 2012; Naeser et al., 2012; Rubi-Fessen et al., 2015; Weiduschat et al., 2011). The reported language gains are diverse and concern auditory and reading comprehension, repetition, naming and spontaneous speech. In several studies, rTMS was combined also with SLT (e.g., Rubi-Fessen et al., 2015; Seniów et al., 2013) as an adjunct treatment to maximize therapy effects.

Prior to conceptualizing new rTMS studies in the area of post-stroke aphasia rehabilitation, it is important to critically appraise the existing literature on the topic. This will allow future researchers and rehabilitation practitioners to identify gaps that require further investigation. Systematic reviews aim to address these problems by identifying, critically evaluating and integrating the findings of all relevant, high-quality individual studies on the topic. In fact, systematic reviews are considered rigorous, transparent and comprehensive summaries of the best available evidence on what works (Hanley & Winter, 2013). Yet, conducting a systematic review is a resource-intensive process which involves a number of practical challenges. In particular, the way in which systematic reviews are planned and conducted can be subject to a range of biases that can compromise the quality of the systematic review and the reliability of the findings (Shea et al., 2017).

The aim of the present study was to analytically evaluate the quality of the evidence on the effects of TMS as a treatment method (stand-alone or adjunct) for stroke-induced aphasia in published systematic reviews on the topic. The AMSTAR 2 **(A Measurement Tool to Assess Systematic Reviews)** (Shea et al., 2017) instrument was used to evaluate the published research. The AMSTAR 2 is a critical appraisal tool used to evaluate the quality of conduct of systematic reviews for healthcare interventions with the primary goal to help researchers, clinicians and policy-makers to distinguish high-quality reviews.

The research questions that further drive this study are threefold:

(1) What is the quality of conduct of systematic reviews on the application of TMS in post-stroke aphasia rehabilitation based on the AMSTAR 2?
(2) Are the reported effects of rTMS on post-stroke aphasia recovery consistent across the systematic reviews?
(3) Is there strong and reliable evidence regarding the positive effects of rTMS for post-stroke aphasia rehabilitation based on the results of the systematic reviews?

Below we report the process followed to identify and critically appraise published systematic reviews on the topic.

Methods

Requirements for inclusion

The present review was based on guidelines following the Cochrane Handbook on Overviews of Reviews (Becker & Oxman, 2008, pp. 607–631). Only published systematic reviews on RCTs (randomized control trials) focusing on the effectiveness of rTMS for post-stroke aphasia rehabilitation were included. Systematic review articles could also be published in languages beyond English known to the authors (e.g., Greek, French or Italian). For a systematic review to be eligible for evaluation, the trials reported in the review had to fulfil a number of predetermined criteria as reported below:

- participants of trials had to be stroke survivors defined within a post-stroke stage (acute/subacute/chronic);
- the interventions applied had to focus on TMS with and/or without SLT;
- the outcome measures used must have included standardized tests for the assessment of aphasia severity and/or assessment of receptive and expressive language skills with and/or without functional communication abilities;
- the control groups had to have been a sham or placebo groups.

Reviews that reported case studies or case series and open-label trials were excluded as were studies focussing on other types of NIBS other than TMS, (e.g., on transcranial direct current stimulation (tDCS)).

Search methods and selection of studies

The search was conducted on the 27 July 2017 for all articles published to that date and a three-step search process was followed. First, a search was performed in databases specific to systematic reviews recommended by internationally respected resources for the conduct of systematic reviews (Cochrane Handbook, Becker & Oxman, 2008):

- Campbell Library of Systematic Reviews
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects

The search terms that were used were ("TMS" OR "brain stimulation") AND "aphasia". It was anticipated that only a small number of reviews would be identified and therefore broad terms were used in this first search. Second, articles published with the 27th of July 2017 as a cut-off date in Scopus, CINAHL and PubMed were reviewed. All identified records were screened, by two independent researchers, at the title and abstract level using the pre-defined eligibility criteria. Third, all reference lists of the included articles were screened for eligibility. Full texts of all articles meeting the eligibility criteria were retrieved for evaluation by the authors.

Instrument for the assessment of the quality of conduct

To assess the quality of conduct of the included systematic reviews, the AMSTAR 2 instrument (Shea et al., 2017) reported in the appendix was used. The instrument encompasses 10 domains with 16 items (questions) in total. The domains can be broadly grouped into three main areas: (i) quality of reporting; (ii) risk of bias and (iii) methodological quality. In general, the AMSTAR 2 is considered to have adequate content validity, inter-rater reliability and usability (Shea et al., 2017, p. 3), for measuring the quality of conduct of systematic reviews.

The overall confidence rating (high, moderate, low and critically low) applied to the conduct of a systematic review depend on the number of critical and non-critical weaknesses identified after addressing each question in the AMSTAR 2 instrument. **A "yes" answer to a question/item from the instrument is a positive response to adherence to the standard (no weakness); a "no" answer means that no information is provided to rate an item (equals a weakness) and; a "partial yes" refers to instances where it is considered worthwhile to identify partial adherence to the standard, and this is not taken into account when rating the overall confidence in the results of the review.**

Critical weaknesses in the conduct of systematic reviews of RCTs have been identified by Shea et al. (2017, p. 5) as the following (AMSTAR 2 item in parenthesis):

- Not providing an explicit statement that the review methods (protocol) were established before the commencement of the review (item 2)
- Not conducting an adequate literature search (item 4)
- Not providing a justification for excluding individual studies (item 7)
- Not using a satisfactory technique for assessing the risk of bias (ROB) from individual studies being included in the review (item 9)
- Not using appropriate methods for the meta-analysis (item 11)

- Not taking into consideration the risk of bias when interpreting the results of the review (item 13)
- Not carrying out an assessment for the presence of publication bias, and its potential impact on the results of the review (item 15)

For the purposes of our study given the emphasis on the quality of conduct, we also considered the following items as critical weaknesses:

- Not reporting the components of PICO (population, intervention, comparison, outcome) (item1)
- Not performing study selection and data extraction in duplicate (items 5 & 6, respectively)
- Not describing the included studies in detail (item 8)
- Not assessing the potential impact of ROB of a meta-analysis (item 12)
- Not giving a satisfactory explanation for heterogeneity (item14)
- Not reporting any potential sources of conflict of interest, including any funding received for conducting the review (item 16).

We followed the AMSTAR 2 recommendations and considered items “not reporting the selection of study designs for inclusion” (item 3) and “source of funding” (item 10) as non-critical weaknesses.

The overall confidence rating is *high* when none or one non-critical weakness is identified; *moderate* with more than one non-critical weaknesses; *low* with one critical weakness with/without non-critical weaknesses and; *critically low* with more than one critical weakness with/without non-critical weaknesses.

To our knowledge this is the first time the AMSTAR 2 has been used to measure the quality of conduct of systematic reviews on stimulation intervention in aphasia recovery, specifically the application of rTMS, the most extensively applied non-invasive brain stimulation method to date, in cognitive neuroscience (Parkin, Eichtiari, & Walsh, 2015).

Results

Search results

Overall 274 entries (after duplicates were removed) were identified and screened at title and abstract level. Table 1 reports the search strategies followed for PubMed, CINAHL and Scopus.

Fifteen (15) articles were selected for full-text analysis and, four articles were finally included in the review according to the eligibility criteria reported in Figure 1.

Studies that were excluded and a justification for their exclusion from the analysis is reported in Table 2.

Characteristics of the systematic reviews

Up until July 2017, four systematic reviews have explored the effects of low-frequency rTMS for post-stroke aphasia rehabilitation. The research has come from three different countries: Brazil (Gadenz, Moreira, Capobianco, & Cassol, 2015); China (Ren et al., 2014;

Table 1. Search strategies used to access relevant systematic reviews from each database on the application of transcranial magnetic stimulation (TMS) for post-stroke aphasia rehabilitation.

PubMed	((aphasia[Title/Abstract] OR "Aphasia"[Majr])) AND ("Transcranial Magnetic Stimulation"[Majr] OR "transcranial magnetic stimulation"[Title/Abstract] OR TMS[Title/Abstract] OR "theta burst stimulation" OR TBS))) NOT ("transcranial direct current stimulation" OR TDCS)
CINAHL	(MM "Aphasia") OR TI aphasia OR AB aphasia) AND (MM "Transcranial Magnetic Stimulation") OR TI (transcranial magnetic stimulation OR TMS OR theta burst stimulation or TBS) OR AB (transcranial magnetic stimulation OR TMS OR theta burst stimulation or TBS) NOT (transcranial direct current stimulation OR TDCS)
Scopus	(TITLE-ABS-KEY (aphasia) AND TITLE-ABS-KEY ("transcranial magnetic stimulation") OR TMS OR "theta burst stimulation" OR TBS) AND NOT TITLE-ABS-KEY ("transcranial direct current stimulation" OR TDCS)

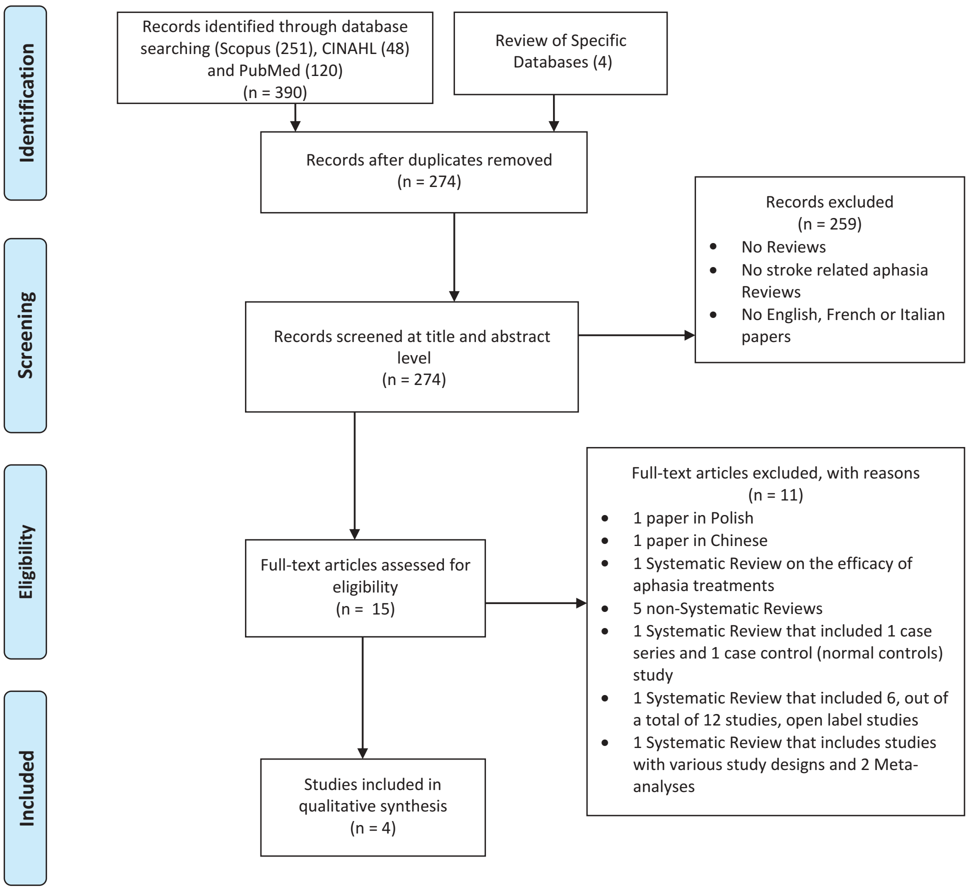

Figure 1. PRISMA flowchart used to identify studies to be included in the qualitative analysis.

Li, Qu, Yuan, & Du, 2015) and Italy (Sebastianelli et al., 2017). Furthermore, meta-analyses were performed to explore the effects of rTMS on post-stroke aphasia in two systematic reviews (Li et al., 2015; Ren et al., 2014); while for the other two systematic reviews, one had a primary focus on communication and deglutition disorders (Gadenz et al., 2015) and one focussed on general stroke motor deficits (hand/arm/leg motor impairment, spasticity, aphasia, visuospatial neglect and dysphagia) (Sebastianelli et al., 2017).

Table 2. A list of the research articles excluded from the analysis, and the justification for their exclusion.

List of excluded articles	Justification for exclusion
(1) Allen, Mehta, Andrew McClure, and Teasell (2012).	Systematic review on the efficacy of general aphasia treatments
(2) Gallletta, Rao, and Barrett (2011).	Not a systematic review
(3) Heiss & Thiel (2012).	Not a systematic review
(4) Kapoor (2017).	Systematic Review that included 1 case series and 1 case control (normal controls) study
(5) Lefaucheur (2006).	Not a Systematic Review
(6) Martin et al. (2009).	Not a Systematic Review
(7) Mendoza et al. (2016).	Systematic Review including studies with various study designs and 2 meta-analyses
(8) Naeser et al. (2010).	Not a Systematic Review
(9) Waldowski, Seniów, Bilik, and Członkowska, (2009).	Paper written in Polish
(10) Wang et al. (2014).	Paper written in Chinese
(11) Wong & Tsang (2012).	A systematic review that included 12 studies: 6 of them were open label studies

Nonetheless, the studies of Gadenz et al. (2015) and Sebastianelli et al. (2017) were included in the analysis as results on the effects of rTMS on post-stroke aphasia were individually described. The characteristics of each systematic review are described in detail in Table 3.

In total, 26 RCT studies were reviewed in the four systematic reviews, but 14 of those studies were duplicates, leaving 12 original studies that included, in total, 174 participants with post-stroke aphasia who received rTMS for aphasia rehabilitation.

Procedure to evaluate the quality of the conduct of each systematic review

The criteria from the AMSTAR 2 instrument were considered for the evaluation of each systematic review, and the appraisal team (authors) recorded their judgements and rankings privately. The AMSTAR 2 guidance document was consulted for interpreting weaknesses detected in critical and non-critical items. The rankings were later aggregated and any differences of opinion during the whole process were discussed until a consensus was reached to derive the team judgement for each systematic review. The results are reported in Table 4 and reveal that the studies of Gadenz et al. (2015), Sebastianelli et al. (2017) and Ren et al. (2014) include more than one critical weakness. On the other hand, Li et al. (2015) had one critical weakness.

The findings suggest that the overall confidence in the quality of the conduct of the systematic reviews as reported in Table 5 is low for one (Li et al., 2015) and critically low for the remaining three (Gadenz et al., 2015; Ren et al., 2014; Sebastianelli et al., 2017).

Discussion

The aim of this study was to evaluate the quality of the conduct of four (4) systematic reviews on RCTs that assess the effects of rTMS for post-stroke aphasia rehabilitation. According to Shea et al. (2017, p. 1), ‘systematic reviews provide an opportunity to base decisions on accurate, succinct, credible and comprehensive summaries of the best available evidence on the topic’. Our goal was to determine if the systematic reviews

Table 3. Detailed summary of the method and results of the research studies on the application of rTMS in post-stroke aphasia rehabilitation included in each systematic review.

Systematic review (references)	Type	Total number of studies & participants	Stroke time-line and aphasia type	Experimental groups	Intervention	Control groups	Outcome Measures	Major findings on recovery of language abilities	Side effects
Gadenz et al. (2015)	RCTs	4 studies 54 adult patients in total receiving real rTMS 52 adult patients in total receiving sham rTMS All right-handed	Subacute Different aphasia-types All with left H lesions stroke Mainly ischemic	Between 6–20 post-stroke individuals with aphasia MA range: 61.8–69.8 years Between 0–2 dropouts	All applied 1 Hz rTMS, 90% RMT 20–30 min per day 8–15 sessions Use of the figure-of-8 coil Stimulation over Broca's homologue	Between 4–20 individuals with post-stroke aphasia receiving sham rTMS MA range: 59.7–71.2 years Between 0–4 dropouts	1 study used the BDAE 2 studies used the AAT 1 study used the CPNT & the ASRS of the BDAE	1 study: improvement in *repetition* in severe aphasia 15 weeks post treatment, 1 study: overall *improvement in AAT scores* and *naming* 1 study: improvement in *naming reaction time* in patients with anterior lesions 15 weeks post treatment 1 study: *overall improvement in AAT scores* but not in subtests	None
Li et al. (2015)	RCTs	4 studies 74 adults in total receiving real rTMS 63 adults in total receiving sham rTMS Most participants were right handed MA range: 60.7–68.8 years	Chronic All aphasia types	Between 6–33 post-stroke aphasic individuals	All studies applied 1 Hz rTMS, 90% RMT 10–30 min per day 10–15 sessions, Stimulation of the right PTr With SLT (3) Without SLT (1)	Between 6–23 post-stroke aphasic individuals Received sham rTMS With SLT (3) Without SLT (1)	1 study used the BDAE 1 study used the AAT & the AVI 1 study used the PNT & the CCAT 1 study used the BDAE & the BNT	Data synthesis showed that 1 Hz rTMS was beneficial for improvement in naming and changes in brain excitability	None

(*Continued*)

Table 3. (Continued).

Systematic review (references)	Type	Total number of studies & participants	Stroke time-line and aphasia type	Experimental groups	Intervention	Control groups	Outcome Measures	Major findings on recovery of language abilities	Side effects
Ren et al. (2014)	RCTs	7 studies 83 adults in total receiving real rTMS 77 adults receiving sham rTMS All right-handed	Acute, Subacute, Chronic All with left H ischemic lesion	Between 6–19 post-stroke aphasic individuals MA range: 60.8–69.8 years	All studies applied 1 Hz rTMS 90% RMT Between 20–30 min per day Between 10–15 sessions, Stimulation of the right PTr, Use of the figure-of-8 coil With SLT (6) Without SLT (1)	Between 4–19 post-stroke individuals with aphasia Received sham rTMS stimulation over the vertex	3 studies used the AAT 1 study used the AAT subtest and total score 1 study used the CPNT 1 study used the BDAE 1 study used the BNT, the BDAE and a picture naming inventory	Data synthesis showed that 1 Hz rTMS was beneficial for post-stroke patients regarding severity of aphasia, naming, writing, repetition and receptive language. Follow-up data reported from 3 of the studies (2 trials followed patients up at 15 weeks post-treatment & 1 study followed up at 2, 8, & 12 months post-treatment) suggest long-term positive effects of rTMS on naming & repetition.	None
Sebastianelli et al. (2017)	RCTs	11 studies 155 adults Received real rTMS Most were right-handed	Acute, Subacute, Chronic, All aphasia types Left H lesion	Between 6–33 post-stroke aphasic individuals MA range: 60.08–69.8 years 1 study did not report MA	10 studies applied 1 Hz rTMS, 90% RMT for 20–30 min per day for 10–15 sessions Over the right PTr/right Broca's homologue, 1 study applied 1 Hz rTMS at 110% RMT, 1000 pulses over the right IFG followed by 20 Hz 10 trains of 5 secs with 30 secs inter-train interval over the left IFG followed by SLT for 10 days	Post-stroke aphasic individuals received sham rTMS	2 studies used the AAT 1 study used the CCAT	Improvement in global aphasia test scores, picture naming and naming accuracy, reaction time, functional communication & auditory comprehension	Not reported

Key: RCTs: Randomized Control Trials; RMT: Resting Motor Threshold; LF: low frequency; PTr: pars triangularis; IFG: inferior frontal gyrus; BDAE: Boston Diagnostic Aphasia Examination; AAT: Aachen Aphasia Test; CPNT: Computerized Picture Naming Test; ASRS: Aphasia Severity Rating Scale; AVI: Activation Volume Indices; PNT: Picture Naming Test; CCAT: Concise Chinese Aphasia Test; BNT: Boston Naming Test; H: hemisphere; MA: mean age

Table 4. Results on the methodological quality of the four systematic reviews reporting the application of rTMS in aphasia recovery based on the AMSTAR 2 checklist.

	Systematic review															
	Gadenz et al. (2015)				Li et al. (2015)				Ren et al. (2014)				Sebastianelli et al. (2017)			
AMSTAR 2 – Checklist 16 questions	Yes	Partial Yes	No	No meta-analysis	Yes	Partial Yes	No	No meta-analysis	Yes	Partial Yes	No	No meta-analysis	Yes	Partial Yes	No	No meta-analysis
1. Did the research questions and inclusion criteria for the review include the components of PICO? (critical)	×				×				×						×	
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (critical)			×			×					×				×	
3. Did the review authors explain their selection of the study designs for inclusion in the review? (non-critical)			×				×				×		×			
4. Did the review authors use a comprehensive literature search strategy? (critical)		×				×				×				×		
5. Did the review authors perform study selection in duplicate? (critical)	×				×				×				×			
6. Did the review authors perform data extraction in duplicate? (critical)	×				×				×				×			
7. Did the review authors provide a list of excluded studies and justify the exclusions? (critical)			×		×						×				×	
8. Did the review authors describe the included studies in adequate detail? (critical)			x			×					x				x	
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (critical)		×			×				×						×	
10. Did the review authors report on the sources of funding for the studies included in the review? (non-critical)			×				×				×				×	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? (critical)				×	×				×							×
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (critical)				×			×			×						×
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (critical)	×				×				×						×	
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (critical)	×				×				×				×			
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (critical)				×	×				×							×
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? (critical)	×				×						×		×			

Key: Yes = all information was provided; No = no information is provided; Partial Yes = partial information was provided

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Table 5. Overall confidence ratings based on the characteristics of each systematic review using the AMSTAR 2 checklist.

	High (none or one non-critical weakness)	Moderate (more than one non-critical weaknesses)	Low (one critical weakness with or without other non-critical weaknesses)	Critically low (more than one critical weakness with or without non-critical weaknesses)
Gadenz et al. (2015)				×
Li et al. (2015)			×	
Ren et al. (2014)				×
Sebastianelli et al. (2017)				×

regarding the application of rTMS to facilitate functional improvement in aphasia are of high quality based on the AMSTAR 2 criteria and whether the translational implications of rTMS on language recovery after stroke is consistent and reliable across the systematic reviews. We address our research questions below.

With regards to our first question on the quality of each systematic review (how they were planned and conducted) as evaluated using the AMSTAR 2 instrument, the results are very **unfavourable**. The finding based on our aggregated confidence ratings was that the overall quality of the conduct of the systematic reviews was in the low range. The systematic review by Li et al. (2015), in which a meta-analysis was performed, was of low quality because the authors failed to assess the potential impact of risk-of-bias (ROB) in the individual studies on their results given they had included RCTs of variable quality. The systematic reviews by Gadenz et al. (2015), Ren et al. (2014) and Sebastianelli et al. (2017) were of critically low quality because of several flaws in critical domains that significantly weaken the confidence that can be placed in this body of work. For example, none reported the methods for the review before the review commenced, and nor did they provide a list of excluded studies and justify the exclusions. Furthermore, Gadenz et al. (2015) and Ren et al. (2014) failed to describe the included studies in adequate detail and only provided brief summaries on the description of participants, interventions, controls, outcomes, design and analysis across the primary studies. **For example, regarding PWA, there was no information on education, employment, socioeconomic status, ethnicity and any co-morbidities, all variables that could have influenced the results of the treatment**. Also, Ren et al. (2014) and Sebastianelli et al. (2017) failed to account for the risk of bias in individual studies when interpreting and discussing the results.

With regards to the second question on the consistency of the **reported** evidence concerning the effects of rTMS on post-stroke aphasia across the systematic reviews, the results are **dissuasive given the irregularities** in the reporting of the data **across** the same studies. To highlight this critical issue, we take the study of Seniów et al. (2013) reported in all four systematic reviews as our comparison study, and note the following in relation to, for example, the PWA descriptors:

- Gadenz et al. (2015) report that all participants were right-handed, whereas no data for handedness for the same study are reported by Li et al. (2015);
- Sebastianelli et al. (2017) and Li et al. (2015) report no data on the type of stroke;
- Ren et al. (2014) did not report the aphasia type;
- Li et al. (2015) provided inaccurate mean age and mean time post-stroke data;

- Li et al. (2015) and Ren et al. (2014) did not report the sex of participants;
- The number of drop-outs in the Senków et al. (2013) study were not reported in the systematic review by Sebastianelli et al. (2017) nor by Li et al. (2015).

In the same way, there were differences between the systematic reviews in relation to reports **from the primary studies** on the **exact** timeline of the rTMS treatment. Within the systematic reviews, there were studies for which treatment was over a period of two to three weeks (weekends excluded), whereas for other studies, treatment was conducted over consecutive days. Only Ren et al. (2014) report treatment timing details accurately.

Moreover, information on stimulation parameters across the systematic reviews was missing. For example, the type of coil used for rTMS was not reported by Sebastianelli et al. (2017) and Li et al. (2015) for the studies included in their respective systematic reviews. Likewise, there were inaccuracies in the reported site of stimulation for studies across all four systematic reviews. For example, Sebastianelli et al. (2017) mention that in the study of Tsai et al. (2014), the site of stimulation was the dorsal anterior pars triangularis (PTr), whereas, for the same study, Li et al. (2015) cite that the stimulation site was PTr generally. Also, Gadenz et al. (2015) and Sebastianelli et al. (2017) cite that in the Waldowski et al. study (2012) the stimulation site was Broca's homologue (this includes PTr and pars opercularis (Pop)). This was indeed the site of stimulation, but Ren et al. (2014) report that the site of stimulation for this study was the PTr only. There were also discrepancies in the reports on outcome measures used in the primary studies. For example, Sebastianelli et al. (2017) cite outcome measures for only 3 out of their 11 included studies. Finally, no systematic review reported information from their included studies on first, the method used to localize the region of interest (RoI) for brain stimulation and second, on the definition of resting motor threshold (RMT).

Our third question on the subject of strong and reliable evidence regarding the positive effects of rTMS for the rehabilitation of aphasia post-stroke, based on the quality of conduct of the systematic reviews, the findings **appear** inconclusive **across language domains (e.g., naming, auditory comprehension, repetition) based on the primary data. For example**, Gadenz et al. (2015) **report improvement in different linguistics domains for some PWA but not for others** (see Table 3). **Similarly**, Li et al. (2015) who performed an additional meta-analysis found that performance in naming improved with changes in brain excitability, but not repetition and auditory comprehension. The researchers contend that low-frequency rTMS in the right hemisphere is effective in terms of naming and reorganization of the left-hemisphere language network. **Likewise**, Ren et al. (2014), who also performed a meta-analysis, support the efficacy of low-frequency rTMS in the right hemisphere with regards to the severity of aphasia, receptive language, naming, repetition and writing. Also, Sebastianelli et al. (2017) observed a considerable variability between studies. They found that low-frequency rTMS improves global aphasia test scores, picture naming and naming accuracy, reaction time, functional communication, and auditory comprehension. But the shift of activation to the damaged hemisphere, and response to low frequency (LF)-rTMS may vary with respect to an optimal site within the pars triangularis (PTr).

Overall, it seems that the evidence from **the quality of conduct** of the systematic reviews regarding the **positive** effects of rTMS on **improving** aphasia post-stroke **appears** inconclusive **across language domains. This is because the overall confidence ratings based**

on the characteristics of each systematic review using the AMSTAR 2 checklist was critically low for three studies and low for one study (see Table 5).

Summing up the results of the four published systematic reviews on the topic leaves us with more questions than answers. For example, why do some PWA respond positively to brain stimulation and others do not? Amongst those who benefit, who benefits the most and why? How important is the neural location and extent of the lesion?

There is a crucial need for rigorous research to verify rTMS induced behavioural-language change in PWA with different types and severity of aphasia. In particular, the distinctive types of neuromodulation (excitatory/inhibitory), the potentially effective stimulation sites and optimal parameters, the effect of the duration, and the long-term impact remain challenges to the field. With regards to the latter, only a few RCTs reported follow-up times, something that does not allow for the evaluation of long-term, if any, effects of rTMS on post-stroke aphasia rehabilitation. From our reading of literature, there is evidence that functional changes induced by inhibitory rTMS may occur over a period of many months (Martin et al., 2009; Seniów et al., 2013; Waldowski, Seniów, Leśniak, Iwański, & Członkowska, 2012); therefore, post-treatment follow-up assessments **could** be carried out to measure progress over time. Also, the four systematic reviews included RCTs that applied only low-frequency rTMS. There was one exception, a review of 1 out of 11 studies (Khedr et al., 2014), that used dual hemispheric rTMS. Such TBS paradigms are currently being explored and appear a most promising innovative approach as positive results in aphasia recovery are surfacing (e.g. Griffis et al., 2016; Vuksanović et al., 2015). For this reason, RCTs applying high-frequency rTMS, bihemispheric stimulation (inhibition and excitation), and TBS paradigms need to be explored further to determine whether such protocols are superior, equally or less effective than low-frequency rTMS.

Likewise, the possible contribution of rTMS to pharmacological treatments or whether rTMS could serve as a stand-alone treatment or should only be given as an adjunct to SLT are areas requiring further investigation. Future studies **could** compare PWA receiving rTMS with SLT with PWA receiving rTMS without SLT. Providing SLT to rTMS as an adjunct treatment to rTMS may have a truly synergic action, but it can also mask the actual therapeutic effects of rTMS.

As most RCTs have included right-handed patients with first-time ischemic stroke, the evidence may not be applicable to left-handed stroke patients or those with hemorrhagic stroke. Furthermore, results from the systematic reviews were not subgrouped by aphasic severity and syndrome and there is a need to see whether severity and type of aphasia is a determining factor for the effectiveness of rTMS applications on language recovery (Boyd et al., 2017). Future studies **could** apply accurate methods of localization of regions of interest. Neuronavigation systems are incorporated in most rTMS equipments and allow for precise localization. It is also suggested that studies use the same outcome measures, as different outcome measures do not allow or make a comparison of outcomes between studies challenging (Walker et al., 2017). Currently, the fact that various scales are used across studies shows that there is a lack of consensus with regards to which aphasia scale is the most appropriate. The Boston Diagnostic Aphasia Examination (BDAE: Goodglass, Kaplan, & Barresi, 2001) is widely used in clinical trials (Berthier, 2005). It is therefore suggested that amongst other scales, researchers also administer the BDAE to decrease outcome measure heterogeneity.

Finally, specific functional markers and biomarkers of good responders to brain stimulation treatments need to be explored and established as previous studies (Martin et al., 2009; Senió w et al., 2013) have demonstrated that not all patients with aphasia respond to inhibitory rTMS over the right hemisphere. Combining rTMS with methodologically advanced fMRI techniques in large-scale RCTs may elucidate biomarkers of brain pathology or treatment-induced neurophysiological changes (see Calhoun & Pearlson, 2008). This will lead to individually tailored rTMS protocols and increased treatment efficacy (Kubis, 2016).

Conclusions

In the field of stroke rehabilitation, systematic reviews on the use of noninvasive brain stimulation (NIBS) methods for the treatment of aphasia symptoms post-stroke are based on small numbers of participants, and well-conducted clinical trials are scarce, suggesting that currently there is not sufficient evidence to draw solid conclusions on the positive effects of NIBS on language recovery after stroke.

The present overview identifies the serious need for more research with methodological rigour. Without high quality published descriptions of rTMS interventions, researchers cannot replicate and build on research findings, and clinicians cannot reliably implement interventions that **may have potential benefit** for people with post-stroke aphasia.

Note

1. TBS refers to a rTMS protocol where pulses are applied in bursts of three, delivered at a frequency of 50 Hz and an inter-burst interval of 200 ms (5 Hz).

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Appendix

AMSTAR 2 – Checklist
1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

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