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A systematic review of repetitive transcranial magnetic stimulation in aphasia rehabilitation: leads for future studies

Sophie Arheix-Parras^{1,2,3,†}, Charline Barrios^{1,2,3,†}, Grégoire Python⁴, Mélanie Cogne⁵, Igor Sibon^{6,7},
Mélanie Engelhardt^{1,2,3}, Patrick Dehail^{1,2,3}, Hélène Cassoudesalle^{1,3}, Geoffroy Moucheboeuf^{1,3},
Bertrand Glize^{1,2,3,4,8,†*}

¹ Handicap Activité Cognition Santé, BPH U1219 Inserm, Université de Bordeaux, F-33000 Bordeaux, France

² Institut Universitaire des Sciences de la Réadaptation, Université de Bordeaux, F-33000 Bordeaux, France

³ Department of physical medicine and rehabilitation, CHU de Bordeaux, F-33000 Bordeaux, France

⁴ Faculté de psychologie, Université de Genève, Geneva, Switzerland

⁵ Department of physical medicine and rehabilitation, CHU de Rennes, Rennes, France

⁶ INCIA, CNRS UMR5287, University of Bordeaux, F-33400 Talence, France

⁷ Stroke Unit, Clinical Neurosciences department, CHU de Bordeaux, 33076 Bordeaux, France

⁸ Institute of Neurodegenerative Diseases, CNRS UMR 5293, Université de Bordeaux, F-33000 Bordeaux, France

† SAP, CB and BG contributed equally

***Corresponding author:** Bertrand GLIZE, Place Amélie Raba Léon, service MPR, 33076 Bordeaux, France; bertrand.glize@chu-bordeaux.fr; Phone: +33.556795546 / Fax: +33.556796006

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1 **1. Introduction**

2 Approximately one-third of all patients who have a stroke subsequently experience
3 language difficulties, which are collectively labeled aphasia (Dickey et al., 2010; Pedersen et
4 al., 2004). Aphasia affects patients' functioning, mood, and quality of life, as well as
5 restricting their participation in many activities and their ability to return to work (Carod-Artal
6 & Egido, 2009; Ferro & Madureira, 1997; Mazaux et al., 2013).

7 This dramatic consequence of having a stroke is due to the disruption of language
8 networks, usually caused by a left-brain lesion. Recovery from aphasia is driven by
9 spontaneous neuroplastic mechanisms (i.e., structural and functional changes in the brain) and
10 reorganization of neural networks. Involvement of perilesional left hemisphere (LH) regions
11 in linguistic tasks and/or the activation of the non-dominant hemisphere can have a positive or
12 negative effect on neuroplasticity and thus affect recovery (for a review, see Hartwigsen &
13 Saur, 2017). Indeed, lesions in the LH may lead to cortical disinhibition in perilesional
14 structures, thereby increasing activity in the LH areas involved in language, and this
15 perilesional activation may promote recovery (Cornelissen et al., 2003; Karbe et al., 1998).
16 However, such lesions may also disrupt inter-hemispheric balance, resulting in
17 neuromodulation (for more details, Biou et al., 2019)).

18 Patient recovery may be improved by modulating cortical activity in these areas of the
19 brain, particularly the language areas in the LH (i.e., Broca's area, Wernicke's area, and the
20 motor cortex), or decreasing activity in the homologous contralesional areas. Aphasia
21 rehabilitation may be accelerated by non-invasive brain stimulation (NIBS) technologies, such
22 as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).
23 Repetitive TMS (rTMS) has been used successfully to treat paresis, spasticity, pain, neglect,
24 and dysphagia in patients who have had strokes (for a review, see Lefaucheur et al., 2011).
25 tDCS has positive effects on aphasia rehabilitation and is probably the best tool for a routine
26 approach because it is inexpensive, easy-to-use, and safe (for a review, see Biou et al., 2019).
27 However, in addition to its benefits on patient rehabilitation and management, rTMS can
28 stimulate focal modulations and provide accurate spatial resolution, which may also inform
29 research into how language reorganization develops in patients who have had strokes. rTMS
30 also has few contraindications and side effects (Cogné et al., 2017; Lefaucheur et al., 2011).

31 In 2004, the first studies on using rTMS in aphasia rehabilitation found that inhibitory
32 stimulation (1 Hz) of Broca's homolog had a significant effect in patients with chronic
33 aphasia (Martin et al., 2004; Naeser et al., 2005). Subsequently, many other studies
34 investigated the effects of rTMS on aphasia rehabilitation. In this review, we summarize the

1 information from studies that have used rTMS to treat patients with aphasia, including
2 randomized clinical trials, prospective studies, case reports, and conference papers. We also
3 discuss some of the challenges for future research.

4 **2. Methods**

5 This systematic review followed the PRISMA guidelines (www.prisma-statement.org).
6 We searched MEDLINE via PubMed and Scopus on 30 October, 2020, for English articles
7 published from 1996 to 2020. The following words and phrases were used to search titles,
8 abstracts, and keywords: “aphasia” AND “repetitive transcranial magnetic stimulation” OR
9 “rTMS” OR “Non invasive brain stimulation” OR “NIBS”. Eligible studies involved post-
10 stroke aphasia rehabilitation using rTMS, with or without speech language therapy (SLT). We
11 excluded articles describing primary progressive aphasia, tDCS, and other neuromodulation
12 tools, as well as studies focusing only on the effects of rTMS in healthy subjects. We also
13 excluded literature reviews, but studies within these reviews were assessed to complete our
14 research. Meta-analyses were considered if they included sub-analyses investigating particular
15 procedures (e.g., frequency, dose-dependent effects, or subacute versus chronic post-stroke
16 phases). Restricting our review to randomized clinical trials may not have provided a
17 complete summary of the use and efficacy of TMS in patients with aphasia, so we also
18 included case reports, prospective studies, and conference papers. Two authors (CB and BG)
19 assessed the eligibility of articles. Consensus was achieved by discussion or in consultation
20 with a third author (GM).

22 **3. Results**

23 On 30 October, 2020, we retrieved 352 articles from our literature search, after removing
24 duplicates. A flow chart describing the articles identified in this study is shown in Figure 1.
25 We included seven meta-analyses and 59 studies describing the use of rTMS to treat patients
26 with post-stroke aphasia. Among the 59 studies, there were 23 randomized clinical trials (526
27 patients), 18 prospective studies (213 patients), 17 case reports (28 patients), and one
28 conference paper (11 stroke patients). Moreover, we briefly described one sub-analysis of a
29 randomized clinical trial (Heikkinen et al., 2019). The tables shown in this systematic review
30 summarize the methods and results of the articles listed.

32 *3.1. Randomized clinical trials*

- 1 Table 1 summarizes the randomized clinical trials we identified and presents the main
- 2 characteristics and results of these studies.

Table 1: Design and results of randomized clinical trials

Study design	Number of patients, stage (time since stroke), type of aphasia, and lost to follow-up	Procedure: location, duration, and intensity	Number and frequency of sessions	Sham/control condition	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures, and follow-up	Results
Ren et al., 2019 (double blind)	45 Subacute (4-12 weeks) Global aphasia Lost to follow-up: rTMS-b group = 3 rTMS-w group = 0 sham group = 2 Discontinued intervention: rTMS-b group = 2 rTMS-w group = 0 sham group = 1	rTMS-b group: right PTR rTMS-w group: right pSTG 1 Hz 20 min 80% RMT	15 sessions, five times a week for 3 weeks.	Sham stimulation + SLT	30 min per day. Interval from stimulation: immediately after stimulation. Training: specific training of specific language features (semantic, phonological, syntactic or motor).	WAB (spontaneous speech, auditory comprehension, repetition and naming). Follow-up: at baseline and immediately after 3 weeks of stimulation.	Both stimulated groups showed greater improvements in language scores compared to the sham group. rTMS-b group: inhibition of the right PTR increased scores for spontaneous speech and repetition. rTMS-w group: inhibition of the right pSTG led to significantly higher scores for auditory comprehension and repetition.
Heikkinen et al., 2019 (double blind)	17 Chronic (> 11 months) Five conduction aphasia Eight anomic aphasia One transcortical motor aphasia Three Broca's aphasia Lost to follow-up: 0	Right PTR 1 Hz 20 min 90% RMT Online: picture-naming task	20 sessions, five times a week for 4 weeks, 10 without rehabilitation and 10 combined with ILAT.	Sham stimulation + same behavioral treatment i.e., naming (2 weeks) + ILAT (2 weeks).	3 h/day for a total of 10 days. Interval from stimulation: immediately after stimulation. Training: naming (2 weeks) + ILAT (2 weeks).	WAB, BNT, and ANT. Follow-up: 1 (baseline), 4, and 7 weeks, as well as 3 months after therapy completion.	"ILAT was associated with significant improvement across groups." No significant effect of rTMS.
Hu et al., 2018 (blindness not reported)	40 Chronic (approximately 7 months) Non-fluent aphasia Lost to follow-up: not reported	HF-rTMS 10 Hz (10 patients) or LF-rTMS 1 Hz (10 patients) on right Broca's homolog 10 min 80% RMT	10 sessions, once daily at a regular time.	Sham group (10 patients): sham stimulation + SLT Control group (10 patients): SLT only	30 min per day. Interval from stimulation not reported. Training: naming of objects, pictures and scenes.	WAB with Aphasia Quotient Assessment (overall severity). Follow-up: before, and after treatment, as well as 2 months after treatment.	LF-rTMS group exhibited a more marked improvement than the HF-rTMS group in spontaneous speech, auditory comprehension, and aphasia quotients (severity) immediately after treatment and at 2-month follow-up. Compared to the control group, the HF-rTMS cohort exhibited significant improvement at 2-months post-treatment in repetition and aphasia quotients (severity).

Haghighi et al., 2018 (double blinded)	12 Subacute (1 month after stroke) Broca's aphasia Lost to follow-up: 0	Posterior rIFG 1 Hz 20 min (contradictory information, see Table 4) 100% RMT	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation + SLT	45 min per day Interval from stimulation: "Some minutes after rTMS or sham condition". Training: work on individual linguistic symptoms and linguistic deficits.	WAB with Aphasia Quotient Assessment (overall severity). Follow-up: at baseline and 2 weeks after the intervention.	Significant improvement in both groups for all subscores of the WAB and aphasia quotient. Significant effect of rTMS on speech content only (contradictory information between figure and tables in the manuscript).
Santos et al., 2017 (double blind)	13 Chronic (> 6 months) Seven anomic aphasia Six Broca's aphasia Lost to follow-up: not reported	All patients received tDCS, TMS and sham condition. TMS: right PTr (BA 45) 1 Hz 20 min 90% RMT	One single session.	Sham stimulation	No SLT, only TMS, tDCS and sham.	BNT Follow-up: before and after each stimulation.	Significant difference in the picture naming task after a single session of tDCS and this was also observed for the sham. No statistical the 3 techniques.
Rubi-Fessen et al., 2015 (blinded)	30 Subacute 19 fluent aphasia 11 non-fluent aphasia Lost to follow-up: 0	Right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions in 2 weeks.	Sham stimulation + SLT	45 min Interval from stimulation: immediately after rTMS. Training: oral naming, preactivation of word retrieval, application of increasing cues to support deliberate lexical retrieval, consolidation of successful verbal naming by additional written naming, variation of training stimuli progressing from single object to related action pictures as provided by everyday life activities, exclusion of holistic nonverbal facilitation methods, or both methods that primarily involve RH functions.	AAT, naming task based on Snodgrass and Vanderwart naming test: 60-item, Amsterdam Nijmegen Everyday Language Test, item of the Functional Independence Measure related to communication skill. Follow-up: the day before and the day after treatment.	Both groups improved their language and communication skills. Stimulation group: significant improvements for all 10 measures. Sham group: significant improvements for six of the 10 measures (AAT profile height, AAT repetition, AAT written language, AAT comprehension, naming screening, and Amsterdam-Nijmegen Everyday Language Test). The gain between baseline and post-treatment performance for almost all measures was higher in the real stimulation group.

Yoon et al., 2015 (not blinded)	20 Chronic (approximately 6 months) Non-fluent aphasia Lost to follow-up: 0	rIFG 1 Hz 20 min 90% RMT	20 daily sessions, five times a week for 4 weeks.	SLT only	60 min, twice a week, for 4 weeks Interval from stimulation: immediately after rTMS. Training: conventional SLT, language-oriented treatment consisting of understanding the program via the visual and auditory senses, expression training for spoken language.	WAB (Korean version, oral language domain was used). Follow up: before and after the treatment.	Intra-group analysis only. Significant improvements in repetition and naming in the case group, but no significant improvement was noted in the control group.
Wang et al., 2014 (double blind)	45 Chronic (> 6 months) Non-fluent aphasia Lost to follow-up: TMSsyn = 0 TMSsub = 1 TMSsham = 1	Three groups: 15: TMSsyn (real stimulation combined with a synchronous picture naming task: online model) 15: TMSsub (real stimulation followed by a picture naming activity: off-line model) 15: TMSsham (sham stimulation combined with concurrent naming activity) Right PTR (BA 45) 1 Hz 20 min 90% RMT	10 daily sessions.	Sham stimulation + SLT	60 min, twice a week. Interval from stimulation: SLT shortly after rTMS in addition to picture naming activity. Training: verbal expressive skills (repetition, phonemic training, semantic training, naming, conservation, picture description tasks, and phrase generation tasks). Compensatory modalities were prohibited during training.	Object and action naming (Picture Naming Test from International Picture Naming Database), CCAT (three subcategories: conversation, scene description, and object naming). Follow-up: before treatment, at the tenth session (post 1) and 3 months after the last intervention (post 2).	TMSsyn group: significant improvements in all language tests (greatest improvement). TMSsub group: significant improvement in CCAT score both at post 1 and post 2, as well as conversation at post 1. TMSsham group: improvement in action naming accuracy at post 1 and object naming accuracy at post 2 but not in CCAT score or subtests.

Tsai et al., 2014 (double blind)	56 Chronic (> 3 months) Non-fluent aphasia Lost to follow-up: TMS = 2 Sham = 1	Right PTR (BA 45) 1 Hz 10 min 90% RMT	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation + SLT	60 min Interval from stimulation: within 30 min after rTMS. Training: expression production (semantic and phonemic training, repetition, naming, conversation, picture description tasks, and phrase generation tasks). Compensatory modalities were prohibited during training.	Object and action naming (Picture Naming Test from International Picture Naming Database), CCAT (four subcategories: conversation, scene description, naming objects, expression and repetition). Follow-up: before treatment, 1 day after the tenth session and 3 months after the last intervention.	Experimental group showed significant improvement compared with sham group in overall CCAT scores, object and action naming accuracy and naming reaction times. Changes in the experimental group persisted at 3 months after the intervention. Patients with a lower RMT in the right motor system appeared to benefit the most from inhibitory rTMS (better improvement in action picture naming accuracy).
Khedr et al., 2014 (double blind)	30 Subacute (1-12 weeks) Non-fluent aphasia Lost to follow-up: TMS = 1 Sham = 0	Right Broca's homolog 1 Hz 110% RMT 500 pulses over PTR, 500 pulses over POP Left Broca's area 20 Hz 80% RMT 10 trains 5 trains over PTR, 5 trains over POP	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation + SLT	30 min Interval from stimulation: immediately after rTMS. Training: stimulation of various aspects of the language system. Subtests of BDAE were used for training (naming, repetition, and auditory comprehension).	Hemispheric Stroke Scale, ASRS, Stroke Aphasic Depression Questionnaire- Hospital version, the National Institutes of Health Stroke Scale. Follow-up: baseline, at the tenth session, 1, and 2 months after treatment.	Significant improvement in the Hemispheric Stroke Scale language score, in the Stroke Aphasic Depression Questionnaire-Hospital version and in the ASRS after real rTMS compared with sham.
Chieffo et al., 2014 (double blind)	5 Chronic (> 18 months) Two anomic aphasia One conduction aphasia One Broca's aphasia One transcortical sensory aphasia Lost to follow-up: 0	rIFG Inhibitory (1 Hz) Excitatory (10 Hz, 15 min) 100% RMT	Three sessions for each patient separated by a 6- day washout period.	Sham stimulation + naming task	No SLT, only naming tasks (Snodgrass naming test) immediately before and after rTMS session.	AAT and Snodgrass naming test. Follow-up: administered twice separated by 1 week to ensure a baseline, immediately before and after each rTMS session.	Only the excitatory stimulation (10 Hz) was associated with a significant improvement in naming performance and was significantly more effective than inhibitory stimulation. The 'best responder' to HF-rTMS was "the patient with a large lesion involving the cortical frontal regions and more severe naming deficit".

Garcia et al., 2013 (blindness not reported)	Number of patients not reported Chronic (> 6 months), Non-fluent aphasia Lost to follow-up: not reported	Phase 1: locate "best response" RH cortical ROI: primary motor cortex (M1), POp (BA 44), anterior PTr (BA 45), dorsal posterior PTr (BA 45), ventral posterior PTr (BA 45), pars orbitalis (BA 47). 1 Hz 10 min 90% RMT Phase 2: suppress best response RH ROI: right PTr (BA 45) for most patients 1 Hz 20 min 90% RMT	Phase 1: six sessions, 5 consecutive days, with two sessions on the last day. Phase 2: 10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone	No SLT, only rTMS	BDAE (Cookie Theft picture description subtest, Word Comprehension and Commands), BNT, Snodgrass and Vanderwart, Cognitive Linguistic Quick Test. Follow-up: at baseline, after the tenth stimulation, 2 months and 6 months after the tenth stimulation.	"Patients' performance on picture naming is most consistently facilitated by stimulation of the ventral posterior pars triangularis." "Long-term improvement in performance on standardized language assessment." "The first 20 BNT item and BDAE "naming in categories" subsections demonstrate improvement over time."
Thiel et al., 2013 (double blind)	30 Subacute (approximately 40 days) Four Broca's aphasia 12 Wernicke's aphasia Four global aphasia Four amnesic aphasia Lost to follow-up: TMS = 2 Sham = 4	Right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions (no more detail).	Sham stimulation + SLT	45 min Interval from stimulation: immediately after rTMS. Training: deficit-specific aphasia therapy focused on individual linguistic symptoms.	AAT Follow-up: assessment between 16 and 18 days after the start of treatment.	Significant improvement of the AAT score in the rTMS group. Increases more important for naming, comprehension, TT and writing. More voxels activated in the LH after treatment.

Seniów et al., 2013 (double blind)	40 Subacute (2-12 weeks) Six Broca's aphasia 15 Wernicke's aphasia 17 mixed aphasia Two transcortical mixed aphasia Lost to follow-up: TMS = 1 Sham = 1	Right PTR (Broca's homolog) 1 Hz 30 min 90% RMT	15 sessions, five times a week for 3 weeks.	Sham stimulation + SLT	45 min Interval from stimulation: immediately after each rTMS session. Training: therapy focused on individual linguistic symptoms, expression and comprehension of spoken language.	BDAE (subtests of naming, repetition and comprehension). Follow-up: at baseline, immediately after treatment, as well as 3 and 15 weeks after the completion of therapy.	Significant improvement, but no difference between the groups, either immediately after treatment or during the follow-up assessment in the BDAE-Comprehension test, or repetition. There was a trend toward significance in BDAE naming for the experimental group. Significant effect of rTMS in repetition at follow up for patients with severe aphasia at baseline. In sub-analysis including 20 patients with aphasia (Mirowska-Guzel et al., 2013), "serum BDNF (overall concentration, in patients who improved and in those who did not) was statistically higher in patients who did not undergo the rTMS procedure." "In men with aphasia, after the first 6 h of rTMS-supported rehabilitation, BDNF concentration was lower among rTMS-treated patients than placebo-treated patients. A similar difference was observed in women with aphasia after 3 weeks of rTMS-supported rehabilitation."
Heiss et al., 2013 (double blind)	29 (+ two left-handed patients not included in the group analysis). Subacute (< 3 months) Seven Broca's aphasia 12 Wernicke's aphasia Eight amnesic aphasia Four global aphasia Lost to follow-up: not reported Discontinued intervention: 10	Right-handed: right PTR (BA 45) 1 Hz Left-handed: left PTR (BA 45) 1 Hz 20 min 90% RMT	10 sessions (no more detail).	Sham stimulation + SLT	45 min Interval from stimulation: immediately after rTMS. Training: activated networks in the dominant hemisphere.	AAT Follow-up: at baseline and assessment between 16 and 18 days after the start of treatment.	Significantly better recovery of language function in global aphasia test scores and naming-picture performance for right-handed patients treated with rTMS than those who were treated with sham. Shift of activation toward the ipsilesional hemisphere for treated right-handed patients (significant effect). Both left-handed patients also improved.
Barwood et al., 2013 (double blind)	12 Chronic (> 24 months) Non-fluent aphasia Lost to follow-up: not reported	Right PTR (BA 45) 1 Hz 20 min 90% RMT	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone.	No SLT, only rTMS.	BNT, subsets of BDAE and Snodgrass and Vanderwart naming test. Follow-up: 1 week prior to stimulation and at intervals of 1 week, 2 months, 8 months and 12 months post treatment.	Significant changes were observed up to 12 months post stimulation in naming performance, language expression and auditory comprehension compared to the sham group.

Medina et al., 2012 (double blind)	10 Chronic (> 6 months) Non-fluent aphasia Lost to follow-up: not reported	Phase 1: rIFG Motor cortex corresponding to the mouth, POp (BA 44), 3 parts of the PTr (BA 45), pars orbitalis (BA 47) Phase 2: Nine patients: Right PTr (BA 45) One patient: Right pars orbitalis (BA 47) 1 Hz 90% RMT	Phase 1: Six sessions, over 5 consecutive days (two stimulations one the final day) toward different sites of the rIFG to identify the optimal target. Phase 2: 10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone.	No SLT, only naming tasks before and after each stimulation of phase 1.	Cookie Theft Picture Description of the BDAE, and naming tasks. Follow-up: three times at the start of the study and 2 months after the end of the study.	Significant increase in multiple measures of discourse productivity for all patients who received real rTMS. No significant increase in measures of sentence productivity or grammatical accuracy. No significant increase from baseline in patients who received the sham treatment.
Waldowski et al., 2012 (double blind)	26 Subacute (< 3 months) Six Broca's aphasia Six Wernicke's aphasia 12 mixed aphasia Two transcortical mixed aphasia Lost to follow-up: 0	Right PTr (BA 45) (15 min) Right POp (BA 44) (15 min) 1 Hz 30 min 90% RMT	15 sessions, five times a week for 3 consecutive weeks.	Sham stimulation + SLT	45 min Interval from stimulation: immediately after rTMS. Training: expression and comprehension of spoken language, rehabilitation focused on specific training to stimulate various aspects of the language system.	CPNT, subtests of BDAE (naming, repetition, and auditory comprehension), ASRS. Follow-up: at baseline, immediately after 3 weeks of experimental treatment, and 15 weeks after the end of therapy.	No significant differences between the rTMS and sham stimulation groups in the CPNT. However, the rTMS subgroup with a lesion including the anterior part of the language area showed greater improvement in naming reaction time at follow-up and also showed improvement in functional communication abilities.
Kindler et al., 2012 (double blind)	18 Subacute and chronic (> 0.5 months) 12 anomic aphasia Five Broca's aphasia One unclassified aphasia Lost to follow-up: not reported	Right Broca's homolog (BA 45) cTBS 30 Hz 90% RMT	Two sessions on 2 different days separated by 1 week.	Sham stimulation alone.	No SLT, only rTMS	Snodgrass and Vanderwart naming test and subtest of Test of Attentional Performance (assessment of alertness). Follow-up: same day before and after the intervention, precise interval not reported.	The real stimulation group showed significantly greater improvements than the sham stimulation group in accuracy and latency in picture-naming. Better effects in the subacute phase. Alertness: no difference between reaction times post TBS and post sham.
Barwood, et al., 2012 (single blind)	12 Chronic (> 24 months) Non-fluent aphasia Lost to follow-up: not reported	Anterior portion of right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions, five times a week for 2 consecutive weeks	Sham stimulation alone.	No SLT, only rTMS	ERP recorded in a two-stimulus: written word-picture semantic judgement task. Follow-up: prior to stimulation (baseline), 1 week, 2 months, 8 months, and 12 months post stimulation.	Active group N400 responses improved over 12 months, accompanied by improvements in the ERP task. Changes were more significant in the semantically incongruent than congruent condition.

Barwood et al., 2011 (double blind)	12 Chronic (> 24 months) Non-fluent aphasia Lost to follow-up: not reported	Anterior portion of right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone.	No SLT, only rTMS	BNT, subtests of the BDAE and CNPT. Follow-up: 1 week prior to stimulation (baseline) and 1 week post stimulation.	Significant improvements in naming accuracy, latency and repetition for the real stimulation group compared with the sham stimulation group.
Barwood et al., 2010 (double blind)	12 Chronic (> 24 months) Mild to severe non-fluent aphasia Lost to follow-up: not reported	Anterior portion of right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions, one session per day for 10 days.	Sham stimulation alone.	No SLT, only rTMS	CPNT, BNT and subtests of the BDAE. Follow-up: 1 week prior to stimulation (baseline) and 2 months post stimulation.	Significant improvements in naming performance, language expression and auditory comprehension for the stimulation group at 2 months post stimulation.
Barwood et al., 2010 (double blind)	12 Chronic (> 24 months) Non-fluent aphasia Lost to follow-up: not reported	Anterior portion of right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone.	No SLT, only rTMS	ERP recorded in a two-stimulus: written word-picture semantic judgement task. Follow-up: at baseline, 1 week and 2 months post stimulation.	Significant improvements were observed (peak amplitude, mean amplitude, and area under the curve of the N400) in the stimulation group compared with the placebo control group at 2 months post stimulation. However, "no changes were identified in the stimulation group compared to the sham group from baseline to 1 week post stimulation". No change in the latency of the N400.

HF: high frequency
LF: low frequency
LH: left hemisphere
RH: right hemisphere
BA: Brodmann area
BDNF: brain-derived neurotrophic factor
ROI: region of interest
ASRS: Aphasia Severity Rating Scale
ANT: action naming test

PTr: pars triangularis
POp: pars opercularis
pSTG: posterior superior temporal gyrus
rIFG: right inferior frontal gyrus
CPNT: computerized picture naming test
ERP: event-related potential
TT: Token Test
TMS: transcranial magnetic stimulation
rTMS: repetitive transcranial magnetic stimulation

ILAT: intensive language-action therapy
WAB: Western Aphasia Battery
AAT: Aachen aphasia test
BNT: Boston naming test
BDAE: Boston diagnostic aphasia examination
CCAT: concise China aphasia test
tDCS: transcranial direct current stimulation

TBS: theta burst stimulation
cTBS: continuous theta burst stimulation
iTBS: intermittent theta burst stimulation
SLT: speech language therapy
RMT: resting motor threshold

1 The methods used in the 23 randomized clinical trials were heterogeneous, with
2 different target areas and various stimulation intensities, frequencies, and durations (Tables 1
3 and 3). No study found that rTMS had a negative effect on patients with aphasia. Among
4 these 23 studies, four did not find that rTMS had a significant effect on language performance
5 (Heikkinen et al., 2019; Santos et al., 2017; Seniów et al., 2013; Waldowski et al., 2012). All
6 four of these studies used low frequency (LF) rTMS at an intensity of 90% of the resting
7 motor threshold. The target areas in these studies were the right pars triangularis (PTr)
8 (Heikkinen et al., 2019; Santos et al., 2017; Seniów et al., 2013; Waldowski et al., 2012) and
9 also the right pars opercularis (POp) for one study (Waldowski et al., 2012). One study
10 involved a single session of rTMS stimulation, not combined with SLT (Santos et al., 2017).
11 Two studies provided 45 min of SLT in the subacute phase (Seniów et al., 2013; Waldowski
12 et al., 2012), and one study provided 3 h of intensive language-action therapy following the
13 rTMS sessions (Heikkinen et al., 2019). The patients in these four studies had different types
14 of aphasia: Broca's aphasia (21 patients), Wernicke's aphasia (21 patients), mixed aphasia (29
15 patients), transcortical mixed aphasia (four patients), conduction aphasia (five patients),
16 anomic aphasia (15 patients), and transcortical motor aphasia (one patient).

17

18 3.2. *Prospective studies and case reports*

19 The methods used in the 36 prospective studies and case reports were also
20 heterogeneous, with different target areas and various stimulation intensities, frequencies, and
21 durations. The 18 prospective studies, 17 case reports, and one conference paper are listed in
22 Tables 2 and 4. No study found that rTMS had a negative effect on patients with aphasia.
23 Among these 36 studies, two did not find that rTMS had a significant effect on language
24 performance (Al-Janabi et al., 2014; Martin et al., 2009). Martin et al., (2009) used 10 daily
25 sessions of LF rTMS to target the PTr. This treatment was not combined with SLT. Al-Janabi
26 et al. (2014) used excitatory intermittent theta burst stimulation (iTBS) to stimulate the right
27 POp. The three sessions of iTBS were followed by melodic intonation therapy to activate the
28 right hemisphere (RH) of the brain.

29

Table 2: Design and results of other studies and case reports

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Versace <i>et al.</i> , 2020 (pilot study)	13 Chronic (2-10 years) Fluent aphasia	Wernicke's area, the homologous temporal area of the right hemisphere and primary visual cortex iTBS 50 Hz 80% AMT	iTBS on the three different cortical regions on separate days.	No training	TT Follow-up: baseline (T0), 5 min after iTBS (T1) and 40 min after iTBS (T2).	"Transient facilitatory effect of a single session of iTBS over Wernicke's area on a simple auditory comprehension task", only at T1. At T2, there was no difference between the groups.
Georgiou <i>et al.</i> , 2019 (cases report)	- Patient 1: Chronic (20 months post stroke) Mild to moderate anomic aphasia - Patient 2: Chronic (25 months post stroke) Severe global aphasia	Right PTr (BA 45) cTBS 50 Hz 80% RMT	10 sessions, 10 consecutive days.	No training	BDAE, Multilingual Assessment Instrument for Narratives, Quantitative Production Analysis Protocol, Stroke and Aphasia Quality of Life Scale 39. Follow-up: prior to treatment, post treatment and 3 months later.	Patient 1: improvement in auditory comprehension, significant improvement of language expression, naming ability remained stable post treatment and at follow-up. Improved quality of life but decreased psychosocial score. Patient 2: improvement in auditory comprehension, significant deterioration in language expression "but at follow-up showed a trend toward improvement". Slight decrease in naming scores post treatment and at follow-up. Significant decrease in psychosocial score.
Harvey <i>et al.</i> , 2019 (prospective study)	11 Chronic (> 6 months) Six anomic aphasia Four Broca's aphasia One conduction aphasia	Right PTr (BA 45) and at the vertex (control site) in separate sessions cTBS 50 Hz 80% RMT	Single session.	No training	Naming accuracy from the International Picture Naming Project. Follow-up: two baselines and after stimulation.	Improvement in naming for individuals with more severe baseline naming impairments. Correlations between the severity of baseline phonological error production, naming improvements, and fewer phonological errors post cTBS. No link between semantic error production and cTBS effects.

Szaflarski <i>et al.</i> , 2018 (feasibility study)	12 Chronic (>12 months) Eight anomic aphasia One global aphasia Two Broca's aphasia One conduction aphasia	Residual left hemispheric language area (Broca) iTBS 50 Hz 80% of AMT obtained from the right hemisphere	10 sessions, one session per day for 10 consecutive weekdays.	45 min Interval from stimulation: immediately after iTBS. Training: modified CIAT administered.	WAB, BNT, Semantic Fluency Test, Controlled Oral Word Association Test, fMRI for language Follow-up: before the treatment (T1), immediately after the treatment (T2), and approximately 3 months later (T3).	"Preliminary safety, feasibility, and efficacy evidence for conducting fMRI guided iTBS therapy" associated with modified CIAT. "Significant effect of session on WAB aphasia quotient and spontaneously correct responses on BNT. Association between improvements in WAB aphasia quotient from T2 to T3 and decreased blood-oxygen-level-dependent signal in left inferior parietal lobe. Improvements in BNT from T1 to T3 with decreased signal in rIFG."
Rossetti <i>et al.</i> , 2018 (case report)	Woman 64 years old Chronic (23 months) Anomic aphasia	Right Broca's homolog 1 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, semantic and phonemic fluency tests. Stroop test to assess executive functions (and exclude nonspecific effect of stimulation). Follow up: 11 months after stroke (baseline, T1), before enrollment (23 months after stroke, T2), immediately after rTMS (T3), and 2 months after rTMS (T4).	Significant improvement in verbal fluency immediately after rTMS (T3) and significant improvement 2 months after treatment (T4). Not improvements in naming and semantic fluency. Performance on the Stroop test did not show a trend toward improvement. Confirmation of the segregation of neural circuitries subtending phonemic and semantic fluency, suggesting selective benefits of rTMS treatment.
Harvey <i>et al.</i> , 2017 (prospective study)	9 Chronic (> 6 months) Non-fluent aphasia	8 in right PTr (BA 45) 1 in right pars orbitalis (BA 47) 1 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No SLT, only naming tasks before and after rTMS in the optimal site-finding phase.	Naming task based on Snodgrass and Vanderwart naming test: 40 item, 20 items repeated across sessions and 20 novel items. Follow-up: before and immediately after rTMS, as well as at 2 and 6 months follow-up.	Significant improvement in naming accuracy immediately after rTMS and 6 months after rTMS. Posterior shift in the recruitment of the rIFG and increase in the number of left hemispheric areas recruited for naming in fMRI tasks.
Ilkhani <i>et al.</i> , 2018 (blind study, no control group)	24 Chronic (> 1 year) Broca's aphasia	Right Broca's homolog 1 Hz 10 min Intensity not reported	10 sessions, frequency not reported.	Not reported.	Naming: images of everyday objects that are not affected by cultural, ethnic, or educational differences. Persian version of the Wechsler test to assess vocabulary comprehension: accuracy score based on correct/incorrect answers. Follow-up: before and after treatment.	Significant improvement in naming accuracy after rTMS. Authors noted significant effect on dysarthria but did not report the precise assessment method used.

Hara <i>et al.</i> , 2017 (single group intervention study)	8 Chronic (> 29 months) One mild-fluent aphasia One moderate-fluent aphasia One severe fluent aphasia One mild non-fluent aphasia One moderate non fluent aphasia Three severe non-fluent aphasia	Two groups: - LH activation: rIFG inhibition 1 Hz 40 min 90% RMT - RH activation: rIFG facilitation 10 Hz 12 min 90% RMT LF-rTMS or HF-rTMS was chosen, depending on cerebral activation during a repetition task.	10 sessions, one session per day except on Sunday.	60 min Interval from stimulation: immediately after rTMS. Training: three main tasks: - describe and answer questions about a photograph and recall the names of objects and scenes shown previously; - words and sentences repetition task; - dictate words and sentences presented by the therapist.	SLTA Follow-up: baseline and 3 months after treatment.	Significant improvement in language function (SLTA total score) after intervention in both groups. No difference in improvement between the groups. Improvement associated with a decrease in interhemispheric imbalance.
Zhang <i>et al.</i> , 2017 (case report)	Woman 39 years old Subacute (4 months after stroke) Conduction aphasia	Left Broca's area 5 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	30 min Interval from stimulation: immediately after Rtms. Training: free talk, correction of mistakes in pronunciation and phonetic annotation of Chinese characters.	WAB Follow-up: 1 month pre-rTMS, 1 week pre-rTMS, 2 weeks post-rTMS, and 2.5 months post-rTMS.	Significant improvements in language ability at 2 weeks post-treatment. Constant increase in gains 2.5 months post-treatment. fMRI: more focused activation pattern and significant activation in the left dominant hemisphere (perilesional areas) relative to the right hemisphere. Increased fractional anisotropy in the left STG, which is important in language processing.
Griffis <i>et al.</i> , 2016 (prospective study)	8 Chronic (> 5 years) Four anomic aphasia (2 with dysarthria and 1 with conduction aphasia). Four non-fluent Broca's aphasia (or 5 with anomic aphasia and 3 with Broca's aphasia: discrepancy between the table and text)	"residual language-responsive cortex in or near the IIFG" iTBS 50 Hz 80% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, Peabody Picture Vocabulary Test, Semantic Fluency Test, Controlled Oral Word Association Test, complex ideation subtest of the BDAE. Follow-up: before stimulation (maximum of 7 days before) and between 14 and 21 days after stimulation.	Leftward shift in IFG activity, decrease in rIFG activation. Significant improvement in the Semantic Fluency Test, non-significant improvements in the BNT, non-significant decrease in performance of the Controlled Oral Word Association Test. No significant change in noun recognition performance pre and post iTBS.

Hara <i>et al.</i> , 2015 (single group intervention study)	50 Chronic (> 6 months) 27 non fluent aphasia 23 fluent aphasia	Two groups: - RH-LF-rTMS group : 29 patients: LF-rTMS 1 Hz on the right non-lesional hemisphere (left compensatory hemisphere for language at fMRI) - LH-LF-rTMS group : 21 patients: LF-rTMS 1 Hz on the lesional left hemisphere (right compensatory hemisphere for language at fMRI). IFG for patients with non- fluent aphasia. STG for patients with fluent aphasia. 40 min 90% RMT	10 sessions, one session per day except Sunday.	60 min Interval from stimulation: immediately after rTMS. Training: Intensive SLT Three main tasks: - describe and answer questions about a short comic and recall the name of objects and scenes shown previously; - word and sentence repetition task; - dictate words and sentences presented by the therapist Communication by gestures or drawing was prohibited.	SLTA (including four subscales speaking, listening, reading, and writing). Follow-up: at the time of admission and at 3 months after treatment.	RH-LF-rTMS group : significant improvement in the total SLTA score correlated with the pre- and post- intervention change of laterality indices in BA 44 shown in single photon emission computed tomography. The changes in SLTA subscores were significantly correlated with changes in laterality indices (in BA 11, 20, and 21 for speaking subscores and in BA 6 and 39 for writing subscores). LH-LF-rTMS group : changes in SLTA subscores were correlated with a pre- and post-intervention performance (BA 10 for speaking subscore and, BA 13, 20, 22 and 44 for reading subscores).
Vuksanović <i>et al.</i> , 2015 (case report)	Man 63 years old Chronic (> 17 months) Severe non-fluent aphasia	First: cTBS (inhibitory) right PTR (BA 45) Immediately after cTBS: iTBS (facilitatory) Broca's area 50 Hz 80% RMT	15 daily sessions.	No training.	BNT, subtests of the BDAE, and the Rey Auditory Verbal Learning Test. Follow-up: before (baseline, T0), 1 week after (T1), and 2 months (T2) after TMS treatment.	Improvements in several language functions (propositional speech, semantic fluency, naming, and auditory comprehension), and in short-term verbal memory and verbal learning. Improvements may be greater than for unilateral intervention.
Martin <i>et al.</i> , 2014 (case report)	- Patient 1 : Chronic (> 6 months) Mild to moderate non- fluent aphasia - Patient 2 : Chronic (> 6 months) Severe non-fluent aphasia	Right PTR (BA 45) 1 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	3 h of modified CIAT (with a break for lunch). Interval from stimulation: immediately after stimulation. Training: naming task with phonological and contextual cues if necessary, color picture card games. Gestures and drawing were prohibited.	BNT, BDAE Follow-up: for both patients, before the treatment, 1-2 months after stimulation. Patient 1: 16 months post stimulation. Patient 2: 6 months post stimulation.	Significant improvement in naming pictures and propositional speech at 1-2 months post treatment. Improvement in naming remained at 6 months post treatment for patient 2 but not at 16 months post treatment for patient 1.

Lu <i>et al.</i> , 2014 (case report, with a control subject)	Man 54 years old Subacute (2 months after stroke) Crossed aphasia	4 weeks for left homologous Wernicke's area 4 weeks for left homologous Broca's area 1 Hz 90% RMT	40 sessions, five sessions a week for 8 weeks.	No training.	WAB (including, fluency, auditory, comprehension, repetition, and naming subtests). Follow-up: before and after homologous Wernicke's area stimulation, before and after homologous Broca's area stimulation and 6 months after treatment.	Significantly reduced structural and functional connectivity. Hypometabolism in RH and left cerebellum. "Stimulating left Wernicke area could improve auditory comprehension. Stimulating left Broca's area could enhance expression. Results outlasted 6 months by 1 Hz rTMS balancing the excitability inter-hemisphere".
Al-Janabi <i>et al.</i> , 2014 (two case reports, with sham treatment)	- Participant GOE: 65 years old Chronic (18 months) Moderate non-fluent Broca's aphasia - Participant AMC: 49 years old Chronic (20 months) Moderate to severe non-fluent Broca's aphasia	GOE: Right PTr (BA 45) AMC: Right POp (BA 44) iTBS 50 Hz 80% RMT	Three sessions, separated by 3 days.	40 min Interval from stimulation: immediately after stimulation. Training: melodic intonation therapy.	Automatic production of verbal sequence and repetition tasks, fMRI during two tasks (automatic speech task and naming/reading task). Follow-up: 1 week before treatment, immediately before the first treatment, after each treatment session and 1 week after completion of the study.	GOE improved significantly in verbal fluency and the repetition of phrases when treated with melodic intonation therapy and TMS. No improvement for AMC. fMRI results: "GOE showed an increase in left Broca's activation from the pre-treatment to post-treatment session," and a "decrease in right Broca's homolog activation." For AMC: increase in the activation of both hemispheres (right Broca's homolog and left Broca).
Dammekens <i>et al.</i> , 2012 (case report)	Woman, 55 years old Chronic (39 months) Non-fluent aphasia	IIFG 10 Hz 80% RMT	15 sessions, five sessions a week for 3 consecutive weeks.	No training.	AAT, continuous EEG during resting state. Follow-up: before, after and 4 months after treatment.	Decrease in rIFG activity post rTMS and normalization of IIFG activity in response to beta-3 frequency band (significant effect). Increase in right supplementary motor area activity in response to beta-3 frequency band. Long-term improvement in repetition tests, naming and comprehension. Increased functional connectivity between the IIFG and rIFG in response to theta and beta-3 frequency bands.
Barwood <i>et al.</i> , 2012 (open protocol case series)	7 Chronic (2-6 years) Non-fluent aphasia	Right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, subtests of BDAE, and computerized naming task. Follow-up: 1 week before stimulation, 1 week, 2 months, and 8 months post stimulation.	Significant improvements in picture naming accuracy and latency, spontaneous elicited speech and auditory comprehension. Improvements observed up to 8 months after TMS application.

Naeser <i>et al.</i> , 2012 (case report)	1 Chronic (12.5 years) Non-fluent aphasia	Right Broca's homolog area 1 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	3 h Interval from stimulation: immediately after stimulation. Training: CILT	Naming probe test, BNT, subtests of the BDAE, action naming picture from Druks and Masterson. Follow-up: before stimulation, 1 and 6 months after the tenth treatment.	Improvement of more than 2 SD BDAE action naming (only observed after the second TMS series, when CILT was included), as well as for naming tools/implements and single word repetition. "On Naming Probe Testing, the time series analysis showed significant improvement on BDAE action naming and tools/implements."
Abo <i>et al.</i> , 2012 (pilot study)	24 Chronic (>15 months) 10 fluent aphasia 14 non-fluent aphasia	Application to the hemisphere contralateral to the activated areas on fMRI during a repetition task. rIFG: 11 patients with non-fluent aphasia lIFG: three patients with non-fluent aphasia rSTG: five patients with fluent aphasia lSTG: five patients with fluent aphasia 1 Hz 40 min 90% RMT	10 sessions, a single session per day except Sunday.	60 min Interval from stimulation: after stimulation (no more detail). Training: improve expressive modality including word production, repetition, naming and writing. Other forms of communication were discouraged.	SLTA Follow-up: 1 week before admission and 4 weeks after discharge. SLTA-ST and WAB Follow-up: 1 week before admission and 1 h after the final stimulation.	Patients with non-fluent aphasia: significant improvements in auditory comprehension, reading comprehension and repetition. Patients with fluent aphasia: significant improvements in spontaneous speech. Note: there is discrepancy between the results shown in Table 2 and the text. The protocol (LF-rTMS combined with intensive ST) is safe may enhance recovery from aphasia.
Naeser <i>et al.</i> , 2011 (prospective study)	8 Chronic (> 18 months) Non-fluent aphasia	Four different RH cortical regions of interest (ROIs): - Right PTr (BA 45) - Right POp (BA 44) - Right motor cortex mouth area -Right STG 1 Hz 10 min 90% RMT	Several single sessions with different brain targets.	No training	Naming performance and response time (base on Snodgrass and Vanderwart picture list). Follow-up: before and immediately after rTMS.	Suppression of right PTr: significant increase in picture naming performance and significant decrease in response time. Suppression of right POp: significant increase in response time, no change in number of pictures named.

Szaflarski <i>et al.</i> , 2011 (prospective study)	8 Chronic (>12 months) Four anomic aphasia Four Broca's aphasia	Residual left Broca's area iTBS 50Hz 80% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, Controlled Oral Word Association Test, Semantic Fluency Test, Complex Ideation subtests from the BDAE and Peabody Picture Vocabulary Test IV. Follow-up: before stimulation and during the week following stimulation.	Significant improvements in semantic fluency. Language improvement was associated with "significant shifts of fMRI signal to the affected hemisphere".
Weiduschat <i>et al.</i> , 2011 (a randomized controlled blinded pilot study)	10 Subacute (18-97 days) Two Broca's aphasia Five Wernicke's aphasia Two global aphasia One amnesic aphasia	Right PTR (BA 45) 1 Hz 20 min 90% RMT	8-10 sessions, five sessions a week for 2 consecutive weeks (mean 9.2).	45 min Interval from stimulation: immediately after stimulation. Training: attempt to activate LH language areas.	AAT and PET during a silent verb generation task. Follow-up: before stimulation and after a 2-week rehabilitation period.	Activation shift toward the RH in the control group. Significant clinical improvements in the AAT for the rTMS group only. No clear linear relationship between the extent of lateral shift and clinical improvements.
Cotelli <i>et al.</i> , 2011 (pilot study, randomized and sham treatment)	3 Chronic (> 12 months) Non-fluent aphasia	Left dorsolateral prefrontal cortex 20 Hz 25 min 90% RMT	20 sessions, five sessions a week for 4 consecutive weeks: 1 patient received real rTMS and SLT for 4 weeks, 2 patients received sham stimulation and SLT for 2 weeks, then real stimulation and SLT for the next 2 weeks.	25 min Interval from stimulation: immediately after stimulation. Training: repetition and reading the target word to facilitate naming, articulatory suppression task.	Neuropsychological battery for reasoning and verbal fluency, AAT, the object and action naming subtests, comprehension and sentence comprehension subtests from the BADA. Follow-up: before stimulation, after the first 2 weeks of treatment, after 4 weeks of therapy, and 12, 24, and 48 weeks after the start of stimulation.	Significant improvements in object naming. Neuropsychological assessments, including formal language assessment (ATT and BADA), showed no changes. Significant effect on treated item post rTMS combined with behavioral therapy, with long-term effects.
Jung <i>et al.</i> , 2010 (case report)	Woman 52 years old Chronic (3 years post stroke) Conduction and crossed aphasia	Left lateral sulcus of the parietal lobe 1 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	WAB, MMSE, and Memory Assessment Scale, fMRI during noun generation and sentence completion tasks. Follow-up: before stimulation and 3 days after the final stimulation.	At baseline, lack of activation in both hemispheres during fMRI tasks. After stimulation, significant activation in the rIFG (Broca's area), posterior temporal gyrus. (Wernicke's area), and parietal lobe during noun generation and sentence completion tasks. Activation of the sensorimotor area and posterior occipital lobe. Cognitive evaluation was not improved but speech evaluation was.

<p>Hamilton <i>et al.</i>, 2010 (case report) (including article corrigendum)</p>	<p>Man 61 years old Chronic (7 years post stroke) Non-fluent aphasia</p>	<p>Phase 1: identification of optimal site: Six sites on the rIFG (motor cortex corresponding to the mouth, POp, dorsal posterior PTr, dorsal anterior PTr, anterior POp/ventral posterior PTr, and pars orbitalis). 1 Hz 10 min 90% RMT</p> <p>Phase 2: administration of rTMS at the optimal site: right dorsal posterior PTr (BA 45, greatest improvement in naming with Snodgrass and Vanderwart items). 1 Hz 90% RMT</p>	<p>Phase 1: Six sessions over 2 weeks.</p> <p>Phase 2: 10 sessions, five sessions a week for 2 consecutive weeks.</p>	<p>No training</p>	<p>Subtests of BDAE (Cookie Theft Picture description and picture naming), WAB (only over the 5 years preceding the patient's participation and also 10 months after stimulation). Follow-up: before the stimulation and 2, 6 and 10 months after the stimulation.</p>	<p>Improvement in picture naming, with significant improvement in the naming actions, animals and tools Improvement in picture description at 2, 6, and 10 months after rTMS. Significant improvement on the WAB subscale for spontaneous speech.</p>
<p>Kakuda <i>et al.</i>, 2010 (case series pilot study)</p>	<p>4 Chronic (> 5 months) Mild to moderate motor-dominant aphasia</p>	<p>- Two patients: right frontal lobe - Two patients: left frontal lobe Area homologous to the most active area during pretreatment fMRI in a word repetition task 1 Hz 20 min 90% RMT</p>	<p>10 sessions, one or two sessions per day for 6 consecutive days: two sessions separated by a 7-h rest period on days 2-5, with a single session on the day of admission.</p>	<p>60 min Interval from stimulation: the rest period of 7 h. Training: not reported.</p>	<p>WAB, SLTA and SLTA-ST. Follow-up: 1 week before admission, 1 h after the final rTMS session and 4 weeks after discharge.</p>	<p>In patients with moderate aphasia: improvement in language functions for all three tests (WAB, SLTA, and SLTA-ST). The score increased in some categories of these scales in the patient with mild aphasia. At 4 weeks after discharge, any decreases in improved scores were recorded.</p>

Naeser <i>et al.</i> , 2010 (pilot study)	2 Chronic (> 6 months) Mild and severe non-fluent aphasia	<p>Phase 1: Target: locate "best response" (at least 2 SD above baseline for Snodgrass and Vanderwart naming test after 10 min rTMS). RH cortical ROI among the M1, mouth, and four subregions within right Broca's area (PTr posterior, POp, PTr middle, and PTr anterior). 1 Hz 20 min 90% RMT of the first interosseous muscle.</p> <p>Phase 2: suppress best response RH ROI: usually right PTr (BA 45) 1 Hz 20 min 90% RMT</p>	Phase 2: 10 sessions, five sessions a week for 2 consecutive weeks.	3 h Interval from stimulation: immediately after stimulation. Training: CILT.	BNT, subtests of the BDAE. Follow-up: approximately 2 and 6 months after stimulation (baseline not reported).	<p>Patient 1: significant improvements in subtests of the BDAE and the BNT at 1 and 6 months after the tenth treatment. Significant improvement on BDAE action naming. Improvement in BDAE verb action naming, tools/implements, and single word repetition.</p> <p>Patient 2: significant improvement in the BNT and in naming tools/implements. Improvement in BDAE cookie theft picture description.</p>
Naeser <i>et al.</i> , 2010 (case report)	Man 43 years old Chronic (> 6 months) Non fluent aphasia	<p>Phase 1: locate "best response" RH cortical ROI: M1, mouth, and four subregions within right Broca's area 1 Hz 10 min 90% RMT</p> <p>Phase 2: suppress best response RH ROI: Right PTr (BA 45) 1 Hz 20 min 90% RMT</p>	Phase 2: 10 sessions, five sessions a week for 2 consecutive weeks.	No training but treatment for apnea (continuous positive airway pressure) which also improves language (BNT and BDAE scores).	BNT, subtests of the BDAE. Follow-up: 3 and 6 months after stimulation and 2.4 years later.	Significant increase in phrase length, auditory comprehension and BNT score. These improvements were retained 2.4 years after rTMS.

Kakuda <i>et al.</i> , 2010 (case report)	2 Chronic (> 7 months) Sensory dominant aphasia	Wernicke's area 1 Hz 20 min 90% RMT	10 sessions, one or two sessions per day for 6 consecutive days: two sessions separated by a 6-8h rest period on days 2-5, with a single session on the day of admission Then, once per week for 3 months (outpatient treatment).	60 min Six sessions (hospital) then 3 months of outpatient treatment. Interval from stimulation: after simulation (no more details). Training: auditory comprehension, spoken word-picture matching and spoken printed word matching.	TT and subcategories of the SLTA Follow-up: at the start and end of inpatient treatment and at the end of 3 months of outpatient treatment.	Increase in TT scores and subcategories of the SLTA after the inpatient treatment. No decreases during the period of outpatient rTMS treatment.
Martin <i>et al.</i> , 2009 (pilot study)	Woman (age not reported) Chronic (12.5 years post stroke) Severe non-fluent aphasia	Right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	3 h Interval from stimulation: immediately after rTMS. Training: CILT	BDAE, BNT Follow-up: at baseline, pre-rTMS (three times) and at 1 and 6 months after stimulation.	Significant improvement in BDAE, action naming, tools/implements and single word repetition.
Martin <i>et al.</i> , 2009 (case report)	- Patient 1: Chronic (> 2 years) Mild moderate non-fluent aphasia. - Patient 2: Chronic (> 2 years) Severe non-fluent aphasia	Phase 1: locate "best response" RH cortical ROI: M1, mouth, PTr anterior, PTr posterior, or POp, 1 Hz 10 min 90% RMT Phase 2: suppress best response RH ROI: Patient 1: right PTr posterior (BA 45) Patient 2: right PTr anterior (BA 45) 1 Hz 20 min 90% RMT	Phase 1: four separate sessions. Phase 2: 10 sessions, five sessions a week for 2 consecutive weeks.	No training	BNT, subtests of the BDAE. Follow-up: Patient 1: before stimulation and at 2, 3, 6, 8, 16, 43 and 46 months after stimulation. Patient 2: before stimulation and at 2, and 6 months after stimulation.	Patient 1: improvement in naming and phrase length persisting for almost 4 years post stimulation. Significant activity in the LH perilesional sensorimotor cortex activation at 16, and 46 months post rTMS. Patient 2: no change in naming or propositional speech post treatment. No new persisting perilesional LH activation across the sessions. Activation persisted in the rIFG, right sensorimotor cortex and mouth at 2 and 6 months post-rTMS.

Heiss <i>et al.</i> , 2007 (conference paper, prospective study)	Three groups: - eight male volunteers. - eleven patients with non-fluent aphasia, subacute (2 weeks after left-sided middle cerebral artery infarction). - seventeen patients with mild to moderate aphasia (due to gliomas in the LH).	IIFG and rIFG 4 Hz 30 s At RMT rTMS online: verb generation task vs rest	Not reported.	No training.	Positron Emission Tomography (PET) and verbal fluency task. Follow-up: not reported.	"Three stroke patients activated rCBF in the left inferior frontal gyrus, eight activated both sides during verb generation. rTMS resulted in increased reaction time latency or error rate with right IFG stimulation in five patients indicating essential language function. In the verbal fluency task these patients had a lower performance than patients with effects of rTMS only over the left IFG, suggesting a less effective compensatory potential of right sided network areas."
Winhuisen <i>et al.</i> , 2005 (prospective study)	11 Subacute (within 2 weeks) One mild verbal amnesia Three moderate and one severe sensoric aphasia Three mild and one moderate global aphasia Two mild sensoric aphasia and also severe expressive aphasia	Right and left IFG at maximal activation on PET during a semantic task. In case of no right inferior frontal activation: right PTr (BA 45). 4 Hz 20% of maximum output (2.1 T) Online stimulation: verbal generation task	Not reported.	No training.	Verbal fluency: "Over each stimulation site, rTMS stimulation was started after 10 words. After the end of the 10-s pulse train, the generation task was continued for another five nouns."	Significant increase of latency during stimulation over the IIFG but not over the rIFG, compared with no stimulation. All patients exhibiting increasing reaction time latency or error rate in the semantic task following right rTMS stimulation also exhibited significant activation in the rIFG in PET scans. "The patients with TMS effect only over the left IFG demonstrated a significantly than better performance in the verb generation task than those with TMS effect over the right IFG."
Naeser <i>et al.</i> , 2005 (open protocol pilot study)	4 Chronic (> 5 years) One anomic/conduction aphasia (recovered Broca) One mild non-fluent aphasia One moderate non-fluent aphasia One severe non-fluent global aphasia	Right PTr (BA 45) 1 Hz 20 min 90% RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	Snodgrass and Vanderwart picture naming task, BNT, subtests of the BDAE. Follow-up: pre- and post- stimulation, 2 and 8 months after the tenth stimulation.	"Significant improvement in picture naming at 2 months post rTMS with lasting benefit at 8 months for 3 patients." Improvements in the number of words per phrase for two of the three non-fluent patients at 2 months post-rTMS. However, no persisting effects at 8 months.

Naeser <i>et al.</i> , 2005 (case report)	Woman 57 years old Chronic (6.5 years after stroke) Severe non-fluent/global aphasia	Phase 1: locate "best response" RH cortical ROI: right PTr, right POp, right posterior superior temporal gyrus and right motor cortex. 1 Hz 10 min 90% RMT Phase 2: suppress best response RH ROI: right PTr (BA 45) 1 Hz 20 min 90% RMT	Phase 2: 10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, subtests of the BDAE. Follow-up: within 2 weeks prior to the first stimulation, as well as 2 and 8 months after the tenth session.	Improvements in picture naming on BNT and BDAE subtests at 2 and 8 months after rTMS.
Martin <i>et al.</i> , 2004 (crossover, double blind, sham controlled)	4 Chronic (> 5 years) Broca's anomic Mild non-fluent Moderate non-fluent Severe non-fluent	Phase 1: locate "best response" RH cortical ROI: rPTr, right POp, right posterior superior temporal gyrus and right motor cortex mouth area 1 Hz 10 min 90% RMT Phase 2: suppress best response RH ROI: right PTr (BA 45) 1 Hz 20 min 90% RMT	Phase 2: 10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, subtests of the BDAE. Follow-up: before stimulation and 2 months after stimulation.	Significant improvement in naming pictures.

RH: right hemisphere
LH: left hemisphere
IFG: inferior frontal gyrus
lIFG: left inferior frontal gyrus
rIFG: right inferior frontal gyrus
PTr: pars triangularis
POp: pars opercularis
STG: superior temporal gyrus
rTMS: repetitive transcranial magnetic stimulation

BA: Brodmann area
SLT: speech language therapy
ROI: region of interest
PET: positron emission tomography
fMRI: functional magnetic resonance imaging
EEG: electroencephalography
HF: high frequency
LF: low frequency

CILT: constraint-induced language therapy
CIAT: constraint-induced aphasia therapy
BDAE: Boston diagnostic aphasia examination
BNT: Boston naming test
AAT: Aachen aphasia test
WAB: Western Aphasia Battery
SLTA: Standard Language Test of Aphasia
MMSE: Mini-Mental State Examination
TT: Token Test

iTBS: intermittent theta burst stimulation
cTBS: continuous theta burst stimulation
rCBF: right cerebral blood flow
SD: standard deviation
AMT: active motor threshold
RMT: resting motor threshold
BADA: battery for the analysis of aphasic disorders

3.3. *Meta-analyses*

All seven meta-analyses included in our systematic review used naming performance as an outcome measure (Table 3). Four of these meta-analyses (T. Li et al., 2020; Y. Li et al., 2015; Ren et al., 2014; Yao et al., 2020) used additional outcome measures, such as auditory comprehension and repetition.

The meta-analysis by Ren et al. (2014) showed that LF rTMS targeting the PTR of the right inferior frontal gyrus (rIFG) significantly improved overall language function and language features such as naming, repetition, writing, and comprehension. The following year, Otal et al. (2015) compared studies that investigated inhibition over the contralesional hemisphere using cathodal tDCS and LF rTMS. Analysis of studies that did not distinguish between subacute and chronic post-stroke patients found that rTMS was clinically effective, whereas tDCS was not. Another meta-analysis (Shah-Basak et al., 2016) that did distinguish between chronic and subacute patients found that only TMS was clinically effective in both patient populations. Bucur et al. (2019) analyzed studies that investigated the long-term effects of NIBS (i.e., tDCS and rTMS). These researchers found that NIBS had a significant medium- to long-term effect (from 1–6 months post-stimulation) on patients with post-stroke aphasia, and they found that rTMS was significantly more effective than tDCS. Li et al. (2020) analyzed 11 studies that investigated high frequency (HF) and LF rTMS, including one study that used only HF rTMS and one study that used both HF and LF rTMS. This meta-analysis found that rTMS had a significant effect on naming accuracy, but only for subacute patients. Moreover, there was no evidence that rTMS had an effect on repetition or auditory comprehension scores. However, the most recent meta-analysis, performed by Yao et al. (2020), concluded that LF rTMS improved language ability, including repetition and comprehension, in both chronic and subacute patients.

Table 3: Results of meta-analyses

Meta-analysis	Number of patients, number of studies	Outcome measures	Standardized mean difference and confidence interval	Conclusions
Yao <i>et al.</i> , 2020	536 patients, 18 studies (chronic aphasia in five studies, subacute aphasia in nine studies).	Naming ability	SMD = 0.38, 95% CI [0.16; 0.60] (13 studies, 339 patients)	LF rTMS improved language ability (repetition, naming, comprehension, and written language). The stimulation was effective at both chronic and subacute stages.
		Repetition ability	SMD = 0.52, 95% CI [0.15; 0.89] (10 studies, 237 patients)	
		Comprehension	SMD = 0.46, 95% CI [0.17; 0.75] (10 studies, 237 patients)	
		Written language	SMD = 0.65, 95% CI [0.23; 1.07] (four studies, 93 patients)	
		Everyday communication	SMD = 0.34, 95% CI [0.01; 0.68] (four studies, 140 patients)	
Li <i>et al.</i> , 2020	384 patients, 11 studies (one study with HF rTMS, one study with high and low rTMS, 10 studies with LF rTMS).	Naming ability	SMD = 0.76, 95% CI [0.16; 1.36]	Significant effect of rTMS on naming accuracy. LF-rTMS had a significant effect on naming scores only at the subacute stage. No significant effect of rTMS on repetition scores. No effect of rTMS on auditory comprehension scores in studies using LF and/or HF rTMS. However, improvements in auditory comprehension observed in the study using HF stimulation and in the study using combined dual-hemisphere rTMS.
		Repetition ability	SMD 0.55, 95% CI [-0.37; 1.48]	
		Comprehension	SMD = 0.45, 95% CI [-0.42; 1.33]	
Bucur and Papagno, 2019 (also investigated effect of tDCS)	439 patients (including 217 who had rTMS), 16 studies (eight TMS and eight tDCS).	Naming accuracy (speech in two studies and WAB scores in one study) at follow-up	SMD = 0.53; 95% CI [0.30; 0.75]	NIBS had a significant medium- to long-term effect (1–6 months post-stimulation) on patients with post-stroke aphasia. “Treatment effects are maintained in time.”
Shah-Bazak <i>et al.</i> , 2016 (also investigated effect of tDCS)	143 patients, eight studies (58 chronic patients, 45 subacute, 37 mixed).	Naming accuracy	Chronic patients: SMD = 0.348, 95% CI [0.14; 0.56] Subacute patients: SMD = 0.667, 95% CI [-0.24; 1.09] All patients: SMD = 0.448, 95% CI [0.23; 0.66]	TMS combined with SLT had a significant effect in both chronic and subacute populations. TDCS combined with SLT was effective in chronic but not subacute populations.

Otal <i>et al.</i> , 2015 (also investigated effect of tDCS)	183 patients, six studies	Naming accuracy	SMD = 0.53, 95% CI [0.23; 0.84]	No evidence that cathodal tDCS was effective, but both inhibitory rTMS and tDCS stimulation had a significant effect when combined with SLT (considering all studies that used LF rTMS or cathodal tDCS over the non-lesioned hemisphere). No adverse events.
Li <i>et al.</i> , 2015	132 patients, four studies	Naming	SMD = 0.51, 95% CI [0.16; 0.86;]	LF-rTMS improves naming ability but not performance in comprehension subtests or repetition scores in patients with post-stroke aphasia. Note: However, a moderate improvement in repetition is reported in the results section of this meta-analysis.
		Repetition	SMD = 0.31, 95% CI [-0.04; 0.65]	
		Comprehension	SMD = 0.31, 95% CI [-0.14; 0.75]	
Ren <i>et al.</i> , 2014	160 patients, seven studies	Severity of impairment	SMD = 1.26, 95% CI [0.80 ; 1.71]	LF rTMS targeting the PTR of the rIFG with or without SLT had a clinically positive effect on patients with aphasia following a stroke. Improvements were observed in overall language function including naming, repetition, writing, and comprehension.
		Naming accuracy	SMD = 0.52, 95% CI [0.18 ; 0.87]	
		Repetition	SMD = 0.54, 95% CI [0.16 ; 0.92]	
		Writing	SMD = 0.70, 95% CI [0.19 ; 1.22]	
		Comprehension (TT / BDAE or AAT)	SMD = 0.58, 95% CI [0.07 ; 1.09] (TT) SMD = 0.32, 95% CI [0.08 ; 0.72] (BDAE/AAT)	

SMD: standardized mean difference

CI: confidence interval

rIFG: right inferior frontal gyrus

PTr: pars triangularis

SLT: speech language therapy

HF: high frequency

LF: low frequency

TMS: transcranial magnetic stimulation

rTMS: repetitive transcranial magnetic stimulation

tDCS: transcranial direct current stimulation

WAB: Western Aphasia Battery

NIBS: non-invasive brain stimulation

TT: Token Test

BDAE: Boston diagnostic aphasia examination

AAT: Aachen aphasia test

3.4. *rTMS procedure: low- vs high frequency stimulation of different brain areas*

To restore the balance between the hemispheres and enhance language production, 34 studies inhibited the rIFG, corresponding to the homolog of Broca's area (Tables 1 and 2). Most of these studies used LF stimulation (1 Hz) to suppress the right PTr, although some studies also used continuous (c)TBS (Georgiou et al., 2019; Harvey et al., 2019; Kindler et al., 2012; Vuksanović et al., 2015). In addition, four studies (Dammekens et al., 2012; Griffis et al., 2016; Szaflarski et al., 2011, 2018) used HF iTBS to stimulate the left inferior frontal gyrus (IIFG), corresponding to Broca's area. One case report (Al-Janabi et al., 2014) used iTBS to activate the rIFG and stimulate the RH with melodic intonation therapy, with mixed results. A further three studies (Hara et al., 2017; Khedr et al., 2014; Vuksanović et al., 2015) used stimulation to affect both the right (inhibition) and left (excitation) hemispheres of the brain. Most studies reported improvements in spontaneous speech, auditory comprehension, repetition, and naming accuracy. Some studies reported a shift in activation to the ipsilesional hemisphere.

One randomized sham-controlled double-blind study (Ren et al., 2019) investigated changes in language performance after stimulating Broca's and Wernicke's homologs with LF rTMS. Both stimulated groups showed greater improvements in language scores than the sham groups, but inhibition of the right PTr improved performance in spontaneous speech and repetition, whereas inhibition of the right posterior superior temporal gyrus led to significantly higher auditory comprehension and repetition scores.

3.5. *SLT*

Ten randomized clinical trials and 22 other studies used magnetic stimulation only. However, 27 studies combined magnetic stimulation with SLT, generally to activate the LH and improve naming, repetition, writing, and the expression and comprehension of spoken language. Some studies involved particular rehabilitation protocols such as melodic intonation therapy (Al-Janabi et al., 2014), intensive language-action therapy (Heikkinen et al., 2019), or constraint-induced language/aphasia therapy (Martin et al., 2014; Martin et al., 2009; Naeser et al., 2012; Naeser et al., 2010; Szaflarski et al., 2018). No study has yet compared the difference between benefits of rTMS with or without SLT.

3.6. *Targeting*

1 In total, 14 studies used the standard international 10–20 electrode positioning system
2 to locate the coil over the target area. One study tried to identify a “hot spot” over the left
3 primary motor cortex using TMS, and stimulated this area (Naeser et al., 2011). A total of 33
4 studies used neuronavigational methods based on magnetic resonance imaging (MRI) or
5 functional (f)MRI. Tables 4 and 5 summarize the locations and rTMS procedures used in
6 these studies. Some studies (Abo et al., 2012; Hara et al., 2015; Kakuda et al., 2010; Martin et
7 al., 2009; Winhuisen et al., 2005) also used functional imaging during linguistic tasks (e.g.,
8 repetition, naming, or semantic tasks) to identify the best hemisphere and area to target.

Table 4: Detailed procedures for clinical trials

Study	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Detailed sham procedure, method for checking blinding (where reported)	Details for localization of stimulation
Ren <i>et al.</i> , 2019	Device: MagPro® Coil: 7 cm, 8-shaped, air-cooling	Number of pulses = 1200 Pulses per train = 1 Hz over 20 min	Sham procedure: used the same coil but placed vertically over the vertex, with the same stimulation parameters used for real stimulation. Checking for patients' blindness: not reported	F4 and CP6 on a standard EEG 10–20 system.
Heikkinen <i>et al.</i> , 2019	Device: Nexstim® stimulator using biphasic pulses Coil: 7 cm, 8-shaped, cooled	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: 7.5 cm nonconductive plastic block (Nextim Spacing Part) with similar sound and feel to real stimulation. Checking for patients' blindness: "The subjects had not received rTMS previously, they could not know whether they were receiving real or sham rTMS."	Not reported
Hu <i>et al.</i> , 2018	Device: MAGSTIM® rapid stimulator Coil: 7 cm, 8-shaped, air cooling, magnetic field induction of up to 2 Tesla	For 10 Hz stimulation over Broca's homolog: Train duration = 2 s Interval = 18 s Number of train events = 30 For 1 Hz over Broca's homolog: 600 pulses in 10 min	Sham procedure: "Coil oriented vertically with respect to the surface of the skull. Patients could hear the sound produced by the stimulator, 1 Hz". Checking for patients' blindness: not reported.	F4 of the extended international 10–20 system for EEG electrode placement.
Haghighi <i>et al.</i> , 2018	Device: MAGSTIM® Coil: 7 cm, double air film coil	Not reported. Moreover, contradictory information regarding the duration of stimulation: 1 Hz for 20 min in the intervention section but for 30 min in the abstract and methods section of the manuscript	Sham procedure: stimulation at the vertex with 100% RMT. The coil was tilted to 90°. Similar sound and feel to real stimulation but with no effect on the underlying cortex. Checking for patients' blindness: not reported.	Not reported
Devido dos Santos <i>et al.</i> , 2017	Not reported	Number of pulses = not reported but calculated as 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: sham coil that appears similar to the real coil placed at the same location. Checking for patients' blindness: not reported.	F8 of the standard international 10–20 system.
Rubi-Fessen <i>et al.</i> , 2015	Device: MAGSTIM® Rapid 2 Coil: double, 7 cm coil	Number of pulses = not reported but calculated as 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: stimulation at the vertex with 90% RMT Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Yoon <i>et al.</i> , 2015	Device: MagPro® Coil: 8-shaped, cooled with air	Number total of pulses = 1200 Pulses per train = 1 Hz continuous over 20min	Sham procedure: no stimulation, SLT only. No blind: patients knew what treatment they were receiving. However, the WAB assessors were blinded.	F8 of the standard international 10–20 system.

Wang <i>et al.</i> , 2014	Device: MAGSTIM® rapid Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: placebo coil with an identical paradigm to the TMSsyn stimulation. Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Tsai <i>et al.</i> , 2014	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min	Sham procedure: placebo coil that delivered less than 5% of the magnetic output with an audible 'click' on discharge. Checking for patients' blindness: "Since none of the patients had ever undergone rTMS, they could not identify whether the stimulation was real or sham."	Target identified using neuronavigation based on individual high-resolution MRI.
Khedr <i>et al.</i> , 2014	Device: MAGSTIM® Model 200 Coil: 9 cm, 8-shaped	Over the right Broca's homolog: Number of pulses = 1000 (500 over right PTr, 500 over right POP). Pulses per train = 1 Hz continuously (duration not reported). Over Broca's area: Number of pulses = 1000 Interval = 30 s 5 times over PTr, 5 times over POP Pulse per train = 10 Hz Train duration = 5 s	Sham procedure: same parameters as real stimulation, coil rotated 90° away from the scalp in the sagittal plane with similar sound and feel to real stimulation. Checking for patients' blindness: "Patients had never experienced rTMS previously, they did not know whether they were receiving real or sham."	PTr: "The anterior stimulation site was 2.5 cm posterior to the canthus along the canther-tragus line and 3 cm superior to this line." POP: "The posterior stimulation site was 4.5 cm posterior and 6 cm superior to the canther-tragus line." Target "was validated in three patients using a 3-dimensional MRI sequence with vitamin E capsules in place".
Chieffo <i>et al.</i> , 2014	Device: MAGSTIM® Rapid 2 Coil: H-coil (no more detail)	Inhibitory: Number of pulses = 900 Pulses per train = 1 Hz continuously (duration not reported) Excitatory: Number of pulses = 800 Pulses per train = 20 Train duration = not reported Interval = 20 s, 40 times	Sham procedure: sham coil placed on the same Brainsway helmet design. Similar sound and feel to the real H-coil but without an effective field. Checking for patients' blindness: patients did not know which stimulation they received, and different personnel were involved in the stimulation sessions.	1.5 cm lateral and 5 cm anterior to the right motor area.
Garcia <i>et al.</i> , 2013	Not reported	Phase 1: Number of pulses = 600 No more detail Phase 2: Number of pulses = 1200 No more detail	Sham procedure: the coil was perpendicular to the skull surface (over the PTr). Checking for patients' blindness: "Owing to the difference in sensory experience between real rTMS and sham TMS, it is plausible that some patients receiving sham TMS may be aware of the arm of the study to which they have been randomized," but "no patient in the sham arm of the study receives real rTMS prior to crossing over into the rTMS arm".	Target identified using neuronavigation based on individual high-resolution fMRI (naming task with oral response).
Thiel <i>et al.</i> , 2013	Device: MAGSTIM® Rapid Coil: double, 7 cm	Number of pulses = not reported but calculated as 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: stimulation over the midline vertex. "Sham procedure was maximal over the sagittal sinus." Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.

Seniów <i>et al.</i> , 2013 (Seniów <i>et al.</i> , 2013) & Mirowska-Guzel <i>et al.</i> , 2013	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped, air-cooled	Number of pulses = 1800 Pulses per train = 1 Hz continuously over 30 min	Sham procedure: “Sham coil that looks similar to the real coil. Sham coil was placed at the same site that was used during the real rTMS.” Checking for patients’ blindness: “It was assumed that because participants had never experienced rTMS, they would not know whether they were receiving real or sham stimulation.”	2.5 cm posterior to the canthus along the canther–tragus line and 3 cm superior to the line.
Heiss <i>et al.</i> , 2013	Device: MAGSTIM® Rapid 2 Coil: double, 7 cm	Number of pulses = not reported but calculated as 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: stimulation over the midline at the vertex with identical skin sensation. “This stimulation affects the superior sagittal sinus and does not reach any language related cortex.” Checking for patients’ blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood <i>et al.</i> , 2013	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train = 1 Hz Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: sham coil, which produced the same noise but not the same sensory sensation as the active coil. Checking for patients’ blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Medina <i>et al.</i> , 2012	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: the coil was perpendicular to the scalp (only the rim of the coil contacted the head), same setup. Checking for patients’ blindness: double blind, no more details.	Target identified using neuronavigation based on individual high-resolution MRI.
Waldowski <i>et al.</i> , 2012	Device: MAGSTIM® rapid Coil: 7 cm, 8-shaped, air-cooled	Number of pulses = not reported but calculated as 1800 Pulses per train = 1 Hz continuously over 15 min, twice.	Sham procedure: air-cooled sham coil with similar appearance, sound, location, and parameters. Checking for blindness: because the patients had never experienced rTMS, they did not know whether they were receiving real or sham rTMS.	Anterior stimulation: 2.5 cm posterior to the canthus along the canther-tragus line and 3 cm superior to this line. Posterior stimulation: 4.5 cm posterior and 6 cm superior to the canther-tragus line.
Kindler <i>et al.</i> , 2012	Device: MagPro® X100 Coil: MC-B70, 8-shaped	Number of pulses = 801 burst = 3 pulses at 30 Hz 267 continuous bursts Train duration = 44 s Interval between bursts = 100 ms	Sham procedure: placebo coil: MC-P-B70 Checking for patients’ blindness: not reported	Between C4 and F8 in the 10–20 electroencephalogram system.
Barwood <i>et al.</i> , 2012	Device: MAGSTIM® Rapid 2 Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: sham coil, identical to the real coil. Checking for patients’ blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood <i>et al.</i> , 2011	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: sham coil identical in shape and size to the real stimulation coil but produced no magnetic field. Checking patients’ for blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.

Barwood <i>et al.</i> , 2010	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: sham coil identical in shape and size to the real stimulation coil but produced no magnetic field. Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood <i>et al.</i> , 2010	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number total of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: sham coil identical in shape and size to the real stimulation coil but produced no magnetic field. Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.

MRI: magnetic resonance imaging
fMRI: functional magnetic resonance imaging
TMS: transcranial magnetic stimulation
rTMS: repetitive transcranial magnetic stimulation
PTr: pars triangularis
POp: pars opercularis

EEG: electroencephalography
BA: Brodmann area
WAB: Western Aphasia Battery
SLT: speech language therapy
RMT: resting motor threshold

Table 5: Detailed procedure for other studies or case reports

Study (design)	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Location of stimulus
Versace <i>et al.</i> , 2020	Device: High power Magstim 200 Coil: 9 cm, 8-shaped	Number of pulses = 600 Pulses per train = 10 bursts of three stimuli at 50 Hz Total duration = 200 s Interval = 10 s	CP5 and CP6 on the standard international 10–20 system.
Georgiou <i>et al.</i> , 2019 (case report)	Device: Magstim® Rapid 2 Coil: 7 cm 8-shaped, double air film coil	Number of pulses = 600 Pulses per train = 3 Train duration = 40 s Interval = 200 ms	Target identified using neuronavigation based on individual high-resolution MRI.
Harvey <i>et al.</i> , 2019 (prospective studies)	Device: Magstim® Super Rapid 2 Coil: 7 cm, 8-shaped	Number of pulses = 600 Pulses per train = 3 Train duration = 40 s Interval = 200 ms	Target identified using neuronavigation based on individual high-resolution MRI.
Szaflarski <i>et al.</i> , 2018 (feasibility study)	Device: Magstim® Rapid 2 Coil: 8-shaped	Number of pulses = 600 Pulses per train = 10 bursts of three pulses at 50 Hz Train duration = 2 s Interval = 10 s	Target identified using neuronavigation based on individual fMRI: semantic decision/tone decision fMRI task.
Rossetti <i>et al.</i> , 2018 (case report)	Device: Neuro MS/D therapeutic variant stimulator® Coil: cooled angular, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously (train duration not reported).	Target identified using neuronavigation based on individual high-resolution MRI.
Harvey <i>et al.</i> , 2017 (prospective study)	Device: MAGSTIM Rapid® Coil: 7 cm, 8-shaped	Treatment phase: Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min Optimal site finding phase: Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min	Target identified using neuronavigation based on individual high-resolution MRI.
Ilkhani <i>et al.</i> , 2018 (double-blind study, no control group)	Not reported	Pulses per train = 1 Hz continuously over 10 min	Not reported

Hara <i>et al.</i> , 2017 (single group intervention study)	Device: MagPro® R30 Coil: 7 cm, 8-shaped	LF-rTMS: Number of pulses = 2400 Pulses per train = 1 Hz continuously over 40 min HF-rTMS: Number of pulses = 2400 Pulses per train = 10 Hz over 12 min	F8 on the extended international 10–20 System for EEG electrode placement.
Zhang <i>et al.</i> , 2017 (case report)	Device: Yiuiride CCY-II, Wuhan® Coil: 90-mm round coil stimulator	Not reported	The crossing point between T3-Fz and F7-Cz on the standard international 10–20 system.
Hara <i>et al.</i> , 2015 (single group intervention study)	Device: MagPro® R30 stimulator Coil: 7 cm, 8-shaped	Number of pulses = 2400 Pulses per train = 1 Hz continuously over 40 min	For patients with non-fluent aphasia, F7/8 on the 10–20 electrode system. For patients with fluent aphasia, CP5/6 on the 10–20 electrode system.
Vuksanović <i>et al.</i> , 2015 (case report)	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	cTBS: Number of pulses = 600 Pulses per train = 50 Hz continuously Train duration = 40 s Interval = uninterrupted iTBS: Number of pulses = 600 Pulses per train = 3 Train duration = 2 s Interval = 8 s	F7 and F8 on the standard international 10–20 system.
Griffis <i>et al.</i> , 2015 (prospective study)	Not reported	Number of pulses = 600 Pulses per train = 3 Train duration = 2 s Interval = 10 s	Target identified using neuronavigation based on individual high-resolution MRI.
Martin <i>et al.</i> , 2014 (case report)	Device: MAGSTIM® Super Rapid HF Coil: 7 cm, 8-shaped, air-cooled	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target identified using neuronavigation based on structural MRI scan.
Lu <i>et al.</i> , 2014 (case report, with a control subject)	Device: MAGSTIM® Rapid 2 Coil: 7 cm, 8-shaped, air-cooled	Number of pulses = 600 Pulses per train = 1 Hz continuously (train duration not reported).	Broca's area identified as BA 44/45 based on the Juelich Histological Atlas.
Al-Janabi <i>et al.</i> , 2014 (two case reports, with sham treatment)	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	Number of pulses = 600 Pulses per train = 50 Hz Pulse per train = 3 Train duration = 2 s Interval = 10 s	Target identified using neuronavigation based on individual high-resolution fMRI.

Dammekens <i>et al.</i> , 2012 (case report)	Device: MAGSTIM® Super Rapid Stimulator Coil: 8-shaped (no more detail)	Number of pulses = 2000 Pulses per train = 200, 10 Hz No more detail	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood <i>et al.</i> , 2012 (open protocol case series)	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target identified using neuronavigation based on individual high-resolution MRI.
Naeser <i>et al.</i> , 2012 (case report)	Device: MAGSTIM® Super Rapid HF Magnetic Stimulator Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target identified using neuronavigation based on individual high-resolution MRI.
Abo <i>et al.</i> , 2012 (pilot study)	Device: MagPro® R30 Coil: 7 cm, 8-shaped	Number of pulses = 2400 Pulses per train = 1 Hz continuously over 40 min	F7/8 or CP 5/6 on the standard international 10–20 system.
Naeser <i>et al.</i> , 2011	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min 1 train	Target identified using neuronavigation based on individual high-resolution MRI. M1 was identified based on muscle response after stimulation.
Szaflarski <i>et al.</i> , 2011 (prospective study)	Device: MAGSTIM® Rapid 2 Coil: 7 cm, 8-shaped	Number of pulses = 600 Pulses per train = bursts of 3 pulses at 50 Hz Train duration = 2 s Interval = 10 s Total duration = 200 s	Target identified using neuronavigation based on individual fMRI: semantic decision/tone decision fMRI task.
Weiduschat <i>et al.</i> , 2011 (a randomized controlled pilot study)	Device: MAGSTIM® Rapid 2 Coil: double 7 cm	Not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Cotelli <i>et al.</i> , 2011 (pilot study, sham condition)	Device: MAGSTIM® Coil: double 7 cm air-cooled	Number of pulses = 2000 Pulses per train = 40 Train duration = 2 s Interval = 28 s Number of train events = 50	Target identified using neuronavigation based on MRI template centered on Talairach coordinates X = -35, Y = 24, Z = 48, corresponding to the left dorsolateral prefrontal cortex (BA 8/9).
Jung <i>et al.</i> , 2010 (case report)	Device: MAGSTIM® Rapid 2 Coil: 9 cm, round coil	Not reported (protocol: Naeser <i>et al.</i> , 2005)	P3 on the standard international 10–20 system.
Hamilton <i>et al.</i> , 2010 (case report)	Device: MAGSTIM® Rapid Device: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz continuously (train duration not reported)	Target identified using neuronavigation based on individual high-resolution MRI.

Kakuda <i>et al.</i> , 2010 (case series pilot study)	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target based on fMRI patient data and identified by an experienced neurosurgeon.
Naeser <i>et al.</i> , 2010 (pilot study)	Device: MAGSTIM® Super Rapid HF Coil: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train = 1 Hz over 20 min Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz over 20 min	Target identified using the frameless stereotaxic system based on individual high-resolution MRI.
Naeser <i>et al.</i> , 2010 (case report)	Device: MAGSTIM® Super Rapid HF Coil: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target identified using the frameless stereotaxic system based on individual high-resolution MRI.
Kakuda <i>et al.</i> , 2010 (case report)	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	Not reported	CP5 on the standard international 10–20 system.
Martin <i>et al.</i> , 2009 (pilot study)	Device: MAGSTIM® Super Rapid HF Coil: 7 cm, 8-shaped	Number of pulses = not reported Pulses per train = 1 Hz continuously over 20 min	Target identified using a frameless stereotaxic system based on individual high-resolution fMRI.
Martin <i>et al.</i> , 2009 (case report)	Device: Not reported Coil: 7 cm, 8-shaped	Not reported	Not reported
Heiss <i>et al.</i> , 2007	Not reported	Not reported	Not reported
Winhuisen <i>et al.</i> , 2005 (prospective study)	Device: MAGSTIM® 200 rapid Coil: 7.6 cm, 8-shaped	Train duration = 10 s (no more detail)	Target identified using neuronavigation based on individual high-resolution MRI.
Naeser <i>et al.</i> , 2005 (open protocol study)	Device: MAGSTIM® Super Rapid HF Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz over 20 min	Target identified using neuronavigation based on individual high-resolution MRI.
Naeser <i>et al.</i> , 2005 (case report)	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min Phase 2: Number of pulses = not reported Pulses per train = 1 Hz over 20 min	Target identified using a frameless stereotaxic system based on individual high-resolution MRI.

<p>Martin <i>et al.</i>, 2004 (crossover, double blind, sham condition)</p>	<p>Device: MAGSTIM® Coil: 7 cm, 8-shaped</p>	<p>Phase 1: Number of pulses = not reported Pulses per train = 1 Hz continuously over 10 min</p> <p>Phase 2: Number of pulses = not reported Pulses per train = 1 Hz over 20 min</p>	<p>Target identified using neuronavigation based on individual high-resolution MRI.</p>
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MRI: magnetic resonance imaging
 fMRI: functional magnetic resonance imaging
 BA: Brodmann area
 TMS: transcranial magnetic stimulation
 rTMS: repetitive transcranial magnetic stimulation
 HF: high frequency
 LF: low frequency
 EEG: electroencephalography
 cTBS: continuous theta burst stimulation
 iTBS: intermittent theta burst stimulation

1 3.7. *Subacute vs. chronic phase*

2 Most of the studies described in this review focused on patients who had chronic
3 disease (i.e., more than 6 months after a stroke). Only 14 studies investigated the effects of
4 rTMS on patients with subacute disease (Haghighi et al., 2018; Heiss et al., 2013; Khedr et
5 al., 2014; Lu et al., 2014; Ren et al., 2019; Rubi-Fessen et al., 2015; Seniów et al., 2013;
6 Heiss et al. 2007; Thiel et al., 2013; Waldowski et al., 2012; Weiduschat et al., 2011;
7 Winhuisen Lutz et al., 2005; Zhang et al., 2017), including eight randomized clinical trials
8 and one study with both chronic and subacute patients (Kindler et al., 2012). Among these 14
9 studies, four did not use SLT (Kindler et al., 2012; Lu et al., 2014; Heiss et al. 2007;
10 Winhuisen et al., 2005). Two studies did not find that rTMS had a significant effect (Seniów
11 et al., 2013; Waldowski et al., 2012), and the study with both patient groups found that rTMS
12 was more effective in treating patients who had subacute disease (Kindler et al., 2012).

14 3.8. *Outcome measures*

15 In most of the studies described in this review, the outcome measure was an
16 assessment of language performance such as naming tasks, fluency, reading, or auditory
17 verbal comprehension. Interestingly, most studies reported a significant improvement in
18 naming performance. Only one study (Georgiou et al., 2019) investigated quality of life.

20 3.9. *Short- vs. long-term effects*

21 In most studies, language performance was assessed before, immediately after, and up
22 to 3 months after treatment. In 27 studies, language performance was assessed after more than
23 3 months. The maximum interval between treatment and language performance assessment
24 was 46 months (Martin et al., 2009). Significant effects were usually found immediately after
25 treatment. Among those studies that found an improvement in language performance
26 immediately after treatment and also performed long-term assessments (i.e., more than 3
27 months), only one study did not report that the effects of rTMS persisted (Naeser et al., 2005).

29 3.10. *Risks of bias*

30 In most of the studies reviewed, patients included suffered from non-fluent aphasia.
31 Only 7 randomized controlled trials (205 patients) versus 12 (321 patients) included patients
32 who suffered from other subtypes of aphasia. Moreover, only a few studies have detailed the

1 linguistic impairments of patients by looking at the different phonological or semantic
2 disorders for example. The same observation is made concerning other cognitive abilities.

3 Furthermore, the size and the localization of the lesion were also often poorly
4 described in the reviewed studies and were rarely taken into account for randomization.

5 Different studies from same research groups seemed to include same patients. This
6 may artificially increase the number of studies that found positive effects of rTMS (Barwood
7 et al., 2011, 2013; Martin et al., 2014; Naeser et al., 2005), as well as the potential risk of
8 unpublished negative results. Meta-analyses seem to have taken into account this possible
9 bias.

10

11

12 **4. Discussion**

13 *4.1. Brain targets, the effects of lesion and/or the pattern of aphasia*

14

15 Most of the studies described in this review targeted anterior language areas,
16 particularly those in the RH. Indeed, Broca's homolog was inhibited in most of the studies.
17 Interestingly, the studies that used tDCS generally targeted left anterior areas, particularly
18 Broca's area or the motor cortex (for a review, see Biou et al., 2019). Even if these two
19 approaches have the same goal of addressing inter-hemispheric imbalance by decreasing
20 activity in the RH or increasing activity in the LH, the real effects of these modulations are
21 unknown. Indeed, the effects of facilitation or inhibition are deduced from changes in the
22 amplitude of motor potentials (Di Lazzaro et al., 2004). However, these effects may differ in
23 other cortices and multiple mechanisms may be involved, such as direct activation of
24 pyramidal neurons (i.e., layer V of the cortex) (Di Lazzaro et al., 2004; Di Lazzaro &
25 Rothwell, 2014). However, rTMS also produces neuromodulation via effects on different
26 types of interneurons, particularly GABAergic interneurons (Di Lazzaro et al., 2018). Hence,
27 outside the motor cortex, the effects of rTMS may be different. This could explain the
28 significant effects of antagonistic procedures on a particular target, such as the significant
29 effect on language performance of inhibitory (1 Hz) or excitatory (10 Hz) stimulation of
30 Broca's homolog observed by Hu et al. (2018). These counterintuitive results may also be due
31 to the proximity of contralesional areas that have an effect on language performance. In a
32 recent study, several RH temporal areas had either positive or negative effect on language
33 performance in patients with chronic disease (Hope et al., 2017). Such antagonistic effects of

1 proximal areas in the right frontal cortex may be important at different stages following a
2 stroke. The temporal reorganization of language networks may also be important. Even if
3 right homologous areas are important in early recovery from a stroke (Hartwigsen & Saur,
4 2017), most studies found that inhibition of these areas was beneficial for both subacute and
5 chronic post-stroke patients. Moreover, Hara et al. found that while inhibitory stimulation
6 over the RH or LH could result in significant language improvement, this correlated with
7 changes in cerebral blood flow in Brodmann area 44 only for RH inhibition (Hara et al.,
8 2015). Such observations provide a better understanding of the dynamic reorganization of
9 language networks following a stroke and, in particular, the precise role of the contralesional
10 hemisphere.

11 Moreover, although most studies targeted contralesional areas, in those studies that
12 targeted the perilesional cortex, the effect of a lesion may depend on the post-stroke stage.
13 Indeed, altered tissue properties can perturb the stimulating currents during TMS (O'Brien et
14 al., 2016). These properties are modified during post-stroke brain reorganization and
15 histological changes. In addition, although the resting motor threshold can be calculated,
16 anatomical variations may influence the real cortical electric field values delivered (Heikkinen
17 et al., 2019). Interestingly, dynamic interactions between histological changes and
18 neuromodulation should also be taken into account because myelin repair depends on
19 neuronal activity (Jia et al., 2019), which may be increased by rTMS.

20 Understanding the effect of a lesion on language network reorganization is crucial to
21 understanding the electrophysiological effects of rTMS. However, only a few studies have
22 tried to modulate neural activity using a functional approach, and MRI data have shown that
23 the targeted areas are not necessarily involved in language tasks (for a review, see Hartwigsen
24 and Saur 2017).

25

26 *4.2. Stimulation and frequency parameters and the interval between SLT and rTMS*

27

28 This review helps to identify some of the crucial factors that may influence the
29 effectiveness of rTMS in aphasia rehabilitation, particularly when rTMS is combined with
30 SLT. First, the effects of rTMS depend on the number of pulses given and the durations of the
31 rTMS sessions. For example, the effects of TBS on excitation in the motor cortex depend on
32 the number of pulses given, and the level of excitation decreases over time (Di Lazzaro et al.,
33 2008). Therefore, to obtain maximum benefit from neuromodulation and enhance the effects

1 of rehabilitation and training, SLT should be performed immediately after rTMS. However,
2 the precise interval between rTMS and SLT was not reported in every study.

4 *4.3. Influence of SLT and factors unrelated to rTMS*

5 Several studies found that, unlike treatment using tDCS, rTMS was effective even in
6 the absence of SLT (for a review, see Biou et al., 2019), suggesting that magnetic fields may
7 have a direct effect on language reorganization, whereas electric current does not. Various
8 procedures were used in these studies to combine rTMS with SLT. However, although a dose-
9 dependent effect of SLT on aphasia rehabilitation is well established (Brady et al., 2016),
10 Heikkinen et al. did not find that rTMS had a significant effect on patients with aphasia when
11 rTMS was combined with 3-h sessions of SLT (Heikkinen et al., 2019). Moreover, the benefit
12 of potentialized rTMS effect by adding SLT following the stimulation has not been proven yet
13 because no study explored a design including SLT + rTMS versus rTMS alone. However,
14 such a design would be deleterious for patients because SLT remains the gold standard and is
15 efficient particularly in the subacute phase. However, this design might be used in chronic
16 patients who no longer make progress with SLT.

17 In most of the studies described in this review, rehabilitation involved naming
18 training or was based on patient's symptoms. However, no particular training method was
19 identified as better than the others. A recent meta-analysis also failed to find significant
20 differences among various rehabilitation methods (Brady et al., 2016). Therefore, future
21 studies should focus on an individualized approach to aphasia rehabilitation and, for
22 neuromodulation, individualized parameters and targets. In our opinion, a crucial challenge is
23 that of determining the best treatment for each patient at each particular time, depending on
24 variation in intrinsic factors (e.g., brain/cognitive reserves, genetic factors, and organization
25 of language networks) and extrinsic factors (e.g., the effects of lesions, environmental factors,
26 and access to care facilities). For instance, patient age may influence the effects of rTMS or
27 TBS on rehabilitation (Di Lazzaro et al., 2008). Indeed, an age-dependent effect on
28 neocortical interneurons has been reported for iTBS (Hoppenrath et al., 2016). Early
29 intervention with rTMS may compensate for low activity in some brain areas. However, sub-
30 analyses of patients grouped according to age were not reported in any of the studies
31 described here, and a recent review found no evidence that patient age had a negative impact
32 on recovery from aphasia (Ellis & Urban, 2016).

33 rTMS should be included in this individualized approach. Indeed, would a patient with a
34 large lesion in the left hemisphere benefit from inhibition or facilitation in the right one?

1 Chieffo et al. (2014) compared inhibition versus facilitation of the right hemisphere. They
2 found improvement after inhibition as well as facilitation, and the patient with the largest
3 lesion involving cortical frontal regions and severe naming impairment has benefited the most
4 from such facilitation. This underlines the bivalent function of right brain areas (Hope et al.,
5 2017), particularly when language networks in the left hemisphere are quasi totally destroyed.

6 Another crucial point which could be considered for future studies is the influence of
7 the severity and the pattern of language impairment. Indeed, the severity of aphasia and its
8 impact on rTMS efficacy is poorly described in studies (Chieffo et al., 2014). The pattern of
9 aphasia should be taken into account. Most of patients included in studies of the present
10 review suffered from non-fluent or Broca's aphasia, but positive effects of rTMS were found
11 whatever the aphasia subtype (Thiel et al., 2013), and studies reporting no effect of rTMS
12 included patients with quasi all subtypes. We recommend that the subtype of language
13 impairment should be considered for randomization and treatment. Indeed, a study tried to
14 individualize the neuromodulation choosing the target and parameters of stimulation using
15 fMRI (depending left or right recruitment in language task) (Hara et al., 2015). But it is now
16 known that language features contribute to the prediction of aphasia recovery (Glize et al.,
17 2017). As for fMRI, an individualized approach could be based on linguistic abilities to
18 manage the choice of parameters and to improve rTMS effects. Is it better to target
19 Wernicke's area for patients with Wernicke's aphasia or is it better to facilitate left motor or
20 frontal areas for patients with non-fluent aphasia, etc.? These questions need more
21 investigations, and the best paths to individualize rTMS treatment should also include clinical
22 and linguistic factors in addition to anatomical and functional ones.

23 Moreover, it has been shown across different post-stroke cognitive consequences that
24 educational levels seem to be associated with less post-stroke cognitive deficits (Nunnari et
25 al., 2014), suggesting that education 'protects' from lesion consequences providing resilience.
26 Other specific cognitive factors have been considered as possibly related to the recovery
27 potential, and for example, new word learning abilities predict the outcome following therapy
28 for anomia in chronic aphasic patients (Dignam et al., 2016). Besides new word learning,
29 attentional capacity is another potential cognitive domain which may be involved in language
30 recovery. The involvement of attentional and executive functions on language performance
31 has been reported on both aphasic and healthy (neurologically unimpaired) speakers. In
32 aphasic speakers, performance declines for instance in several linguistic tasks under shared
33 attention (McNeil et al., 2006; Murray et al., 1997). It has also been suggested that domain-

1 general cognitive control capacity may be related to recovery from aphasia (Brownsett et al.,
2 2014). Such abilities were poorly described in rTMS studies.

3

4 *4.4. Neural effects of rTMS in aphasia*

5 Several studies used fMRI to investigate changes in brain activity caused by rTMS. Indeed,
6 improvements that result from rTMS stimulating the LH (Dammekens et al., 2012; Griffis et
7 al., 2016; Hara et al., 2017; Szaflarski et al., 2011, 2018; Zhang et al., 2017) or inhibiting the
8 RH (Hara et al., 2017; Harvey et al., 2017; Heiss et al., 2013) are apparently associated with
9 modulation of cerebral activity in perilesional areas (Zhang et al., 2017), LH areas that are
10 crucial for language such as the IIFG (Griffis et al., 2016; Harvey et al., 2017) and left inferior
11 parietal lobe (Szaflarski et al., 2018), or right homologous areas (Dammekens et al., 2012;
12 Griffis et al., 2016; Harvey et al., 2017; Szaflarski et al., 2018). Therefore, the observed
13 improvements may be associated with changes in the respective roles of these LH or RH areas
14 or with a decrease in the interhemispheric imbalance (Hara et al., 2017; Heiss et al., 2013;
15 Szaflarski et al., 2011).

16 Little is known about the possible effects of rTMS “in the fourth dimension”, which
17 involves investigating the temporal processes that are important for language tasks using
18 magnetoencephalography or electroencephalography (for temporal aspects of neural processes
19 involved in naming and stroke patients, see Laganaro et al., 2013 (Laganaro et al., 2013)).
20 Indeed, rTMS effects may specifically modulate language processes only within particular
21 time windows. For example, changes in the N400 time window for a semantic judgment task
22 were associated with improvements in aphasic symptoms (Barwood et al., 2012; Barwood et
23 al., 2010). Further studies are needed to understand these relationships.

24 Interestingly, rTMS interferes with the secretion of brain-derived neurotrophic factor
25 (BDNF) (Luo et al., 2017), known to be involved in better recovery (Schäbitz et al., 2007).
26 The BDNF genotype influences the effects of rTMS on motor recovery (Chang et al., 2016)
27 and possibly aphasia recovery (Mirowska-Guzel et al., 2013), and it also modulates the effects
28 of tDCS (Fridriksson et al., 2018). Another challenge is to identify new molecular pathways
29 that could be targeted to improve aphasia recovery and rTMS efficacy. In addition to genetic
30 factors, epigenetic mechanisms such as post-translational modifications of histone proteins
31 and microRNAs (Kassis et al., 2017), recently known as enhancers of plasticity observed
32 during repair processes after stroke, should be explored and might predict better response to
33 NIBS.

34

1 *4.5. Value of rTMS for understanding language reorganization and recovery from*
2 *aphasia*

3 Finally, rTMS is a valuable tool for investigating both language networks in healthy
4 subjects and network reorganization following a stroke in patients with aphasia. Both tDCS
5 and rTMS may be used to clarify the role of the RH in language reorganization. The changes
6 observed in interhemispheric balance due to contralesional homolog activity are not limited to
7 language functions but represent a common phenomenon after a stroke. However, the effects
8 of inhibiting the right homologous language areas, particularly the rIFG, suggest a
9 maladaptive role for the RH in reorganizing the language network. The results of this review
10 suggest that combining rTMS with neuroimaging may improve our understanding of adaptive
11 processes in the healthy and lesioned language network.

12
13 **5. Conclusion**

14 This systematic review summarizes the results of studies investigating the effects of
15 rTMS on patients with aphasia. Although further studies are needed to understand the neural
16 mechanisms involved more fully, our review shows that rTMS can have beneficial effects in
17 post-stroke patients. Recent studies have shown that rTMS may be safely implemented
18 routinely to enhance the rehabilitation of patients with subacute and chronic aphasia. Research
19 using rTMS may also provide valuable insight into the reorganization of language networks.

20
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22
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1 Figure 1

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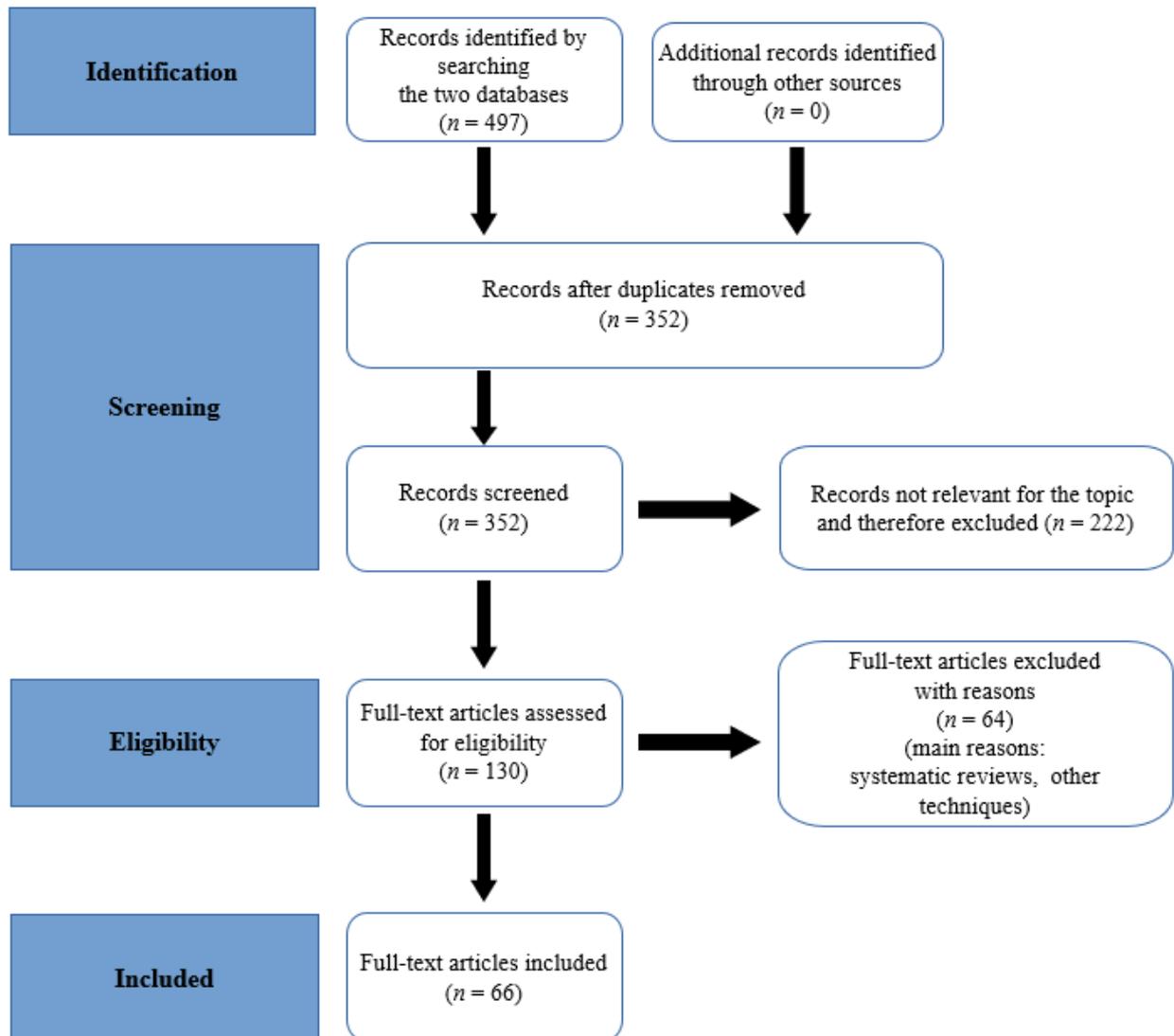
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Flow Diagram
(adapted from PRISMA 2009)



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