REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR MANAGEMENT OF POST-STROKE IMPAIRMENTS: AN OVERVIEW OF SYSTEMATIC REVIEWS

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Objective: To evaluate evidence from published systematic reviews of clinical trials to determine the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in stroke population.

Methods: The Cochrane Library, MEDLINE, CINAHL, EMBASE, and PubMed were searched for systematic reviews up to 15 January 2019. Three authors independently screened the reviews and assessed the methodological quality, using Assessment of Multiple Systematic Reviews (AMSTAR) appraisal tool. Quality of evidence for outcomes evaluated within the reviews was appraised with Grade of Recommendation, Assessment, Development and Evaluation (GRADE) tool.

Results: Twelve reviews (n=9,117 participants) evaluated the effectiveness of rTMS on motor and non-motor (aphasia, depression, dysphagia and cognition) functions. The rTMS protocols applied and outcomes measured were diverse amongst the selected reviews. The findings suggest beneficial effect of rTMS with: “moderate quality” evidence for dysphagia and hemineglect, “low to moderate quality” evidence for motor function (upper limb function, daily activities), and “low quality” evidence for aphasia and post-stroke depression.

Conclusion: Despite widespread use of rTMS, high-quality evidence for its routine use for the treatment of stroke survivors is lacking. Further studies are required to establish differential roles of various protocols and long-term effects of rTMS in the stroke population.

Key words: stroke; transcranial magnetic stimulation; rehabilitation; systematic review.

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troke is a leading cause of long-term neurological disability in adults worldwide, with an estimated 15 million strokes reported annually (1, 2). It frequently causes impairments resulting in long-term debilitating effects (3). Current advances in the medical management of stroke have improved survival rates significantly, and highlight the need for optimal, comprehensive acute and longer-term management of motor and non-motor impairments, which contribute to disability.

Despite spontaneous motor recovery after stroke, at 3 months approximately 70% of stroke survivors continue to have restrictions in functional tasks and activities of daily living (ADLs) due to motor/sensory deficits, incoordination and spasticity (4, 5). During recovery after stroke, abnormal neuronal activity causes disruption in regular interhemispheric communication (6, 7), commonly in the motor system (8). Cognitive impairments (such as post-stroke depression; PSD) are common (reported in almost 30% of patients) (9). Significantly higher rates of PSD and anxiety are reported in chronic stages of stroke recovery, compared with the general population (10). Further, hemispatial neglect (range 13–82%) (11) leads to poor functional motor recovery (12), increased falls risk and caregiver burden (13). Swallowing problems (50–80%) (14), increased length of hospital stay, additional health service utilization, complications and worse outcomes (15). Furthermore, mortality rate significantly increases by 2.6-fold in patients with post-stroke dysphagia compared with their counterparts without dysphagia (16). These impairments contribute to longer-term

LAY ABSTRACT

Stroke causes significant disability and morbidity. Currently, a range of rehabilitation interventions to manipulate or induce brain plasticity, including repetitive transcranial magnetic stimulation (rTMS) are used for stroke care. There is a growing body of research in this area, with several systematic reviews evaluating efficacy and safety of rTMS for various clinical outcomes. This review systematically evaluates evidence from published systematic reviews of clinical trials to determine the effectiveness of rTMS in people with stroke to guide treating clinicians. The included reviews used varied rTMS protocols and outcome measures. The findings suggest limited high-quality evidence for improved motor and non-motor functions following stroke; hence, routine clinical use of rTMS is yet to be established.
morbidity and mortality, restrictions in ADLs, and decreased quality of life (QoL) (17).

Currently, a range of rehabilitation interventions are trialled in the management of stroke. Many alternative and adjunct therapeutic techniques to manipulate or induce brain plasticity, including repetitive transcranial magnetic stimulation (rTMS), are used to enhance conventional rehabilitation therapies (18). rTMS is a non-invasive neuro-modulatory therapeutic intervention used to promote/enhance efficacy of rehabilitation after stroke (19) by restoring the disrupted equilibrium and inter-hemispheric communication to rebalance interhemispheric competition (20). It delivers electrical current to modulate cortical neuronal excitability (5) at the stimulation site (21). Delivering a series of magnetic stimuli to targeted brain areas induces inhibitory effects on motor cortical excitability with low-frequency (LF) (≤1 Hz) or promotes cortical excitability with high-frequency (HF) (≥3 Hz). After stroke, it is postulated that suppression of the undamaged contra-lesional motor cortex by rTMS or increasing the excitability of the damaged hemisphere cortex promotes functional recovery (22). Due to these unique features, the use of rTMS has increased rapidly as a potential rehabilitation tool for stroke patients to enhance functional and psychological recovery (23). However, evidence supporting its routine use for post-stroke impairments is limited (18, 24).

Various systematic reviews have evaluated the effectiveness and safety of rTMS for various functional and psychological outcomes in persons following stroke (9, 18, 21, 25–27). However, published reviews vary in scope, methodology and quality, with different and, at times, diverse findings and conclusions about the effectiveness of rTMS. Further, some review findings overlap with each other. Therapeutic values, including benefit and harm, associated with rTMS, including efficacious approaches, timing, and intensity need to be established. An overview of systematic reviews is a new approach to synthesize high-quality evidence across the same or very similar interventions, to summarize treatment effect in a much broader concept (28). The aim of this review, therefore, is to systematically evaluate evidence from published systematic reviews of clinical trials to determine the effectiveness of rTMS in people with stroke, in order to guide treating clinicians.

**METHODS**

The Cochrane Library database (including Database of Abstracts and Reviews of Effectiveness), MEDLINE, CINAHL, EMBASE, and PubMed were comprehensively searched for systematic reviews evaluating the efficacy of rTMS interventions for various post-stroke impairments until 15 January 2019. The combination of multiple searches for 2 themes of stroke and transcranial magnetic stimulation (non-invasive stimulation) was used for the search strategy. The keywords used to search for studies are listed in Appendix SI1.

A comprehensive multi-pronged methodology was employed. All systematic reviews, meta-analyses registered in these databases that reported a systematic electronic search of literature for a defined period, were included. Bibliographies of pertinent articles and relevant journals were manually searched for additional references. Authors and known experts in this area were contacted as required. Grey literature search was performed using various internet search engines and websites including: System for Information on Grey Literature in Europe, New York Academy of Medicine Grey Literature Collection, National Quality Measures Clearinghouse, and Google Scholar. Systematic reviews on rTMS involving other medical conditions, where data were specifically provided for stroke, were also included. Furthermore, reviews comparing other non-invasive stimulation, such as transcranial direct current stimulation (tDCS), with rTMS, where separate subgroup analysis on the rTMS was included. The exclusion criteria included: reviews conducted in paediatric population (<18 years old); those evaluating the efficacy of interventional rTMS combined with other measures of rehabilitation, pharmacological, surgical intervention; reviews using TMS to assess functional aspects and structure of the brain; non-interventional TMS protocols; non-English reviews; narrative reviews; theses; and reviews listed only in conference proceedings.

**Study selection and data extraction**

Three authors (WK, CR, PH) independently screened all potential abstracts and titles of reviews for inclusion and appropriateness, based on the selection criteria. Each study was evaluated independently, and the full-text article was obtained for assessment to determine whether the review met the inclusion/exclusion criteria. Any disagreement regarding the possible inclusion/exclusion of any individual review was resolved by discussion with other reviewers (BA, FK) and by a final group consensus. Data extraction was conducted by 3 authors (WK, CR, PH) independently, using a standard pro forma. The information obtained from all reviews included: publication and search date, objectives, characteristics of included studies and comparators, findings/patient outcomes in the review, and limitations. Any discrepancies were resolved by final group consensus re-evaluating the review.

**Assessment of the methodological quality of included studies**

Three reviewers (WK, CR, PH) independently assessed the methodological quality of each included review, using the Assessment of Multiple Systematic Reviews (AMSTAR) appraisal tool (Appendix SII1) (29). This critical appraisal tool, with 11 assessment items, has acceptable inter-rater agreement, construct validity and feasibility (29, 30). The Grade of Recommendation, Assessment, Development and Evaluation (GRADE) tool was used to assess quality of evidence for each outcome evaluated within the included reviews on a 4-point scale (high, moderate, 1http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2637

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low and very low quality) (31). First, an a priori ranking of
“high” for randomized controlled trials (RCTs), and “low” for
non-randomized controlled trials was assigned. Then, initial
grading was either downgraded because of the risk of bias, the
inconsistency, the indirectness of evidence or the imprecision
of the publication bias; or upgraded the initial grading because
of a large effect size and consistency in the findings. Finally, the
grade was assigned “very low” if assessment was that the true
effect was likely to be substantially different from the estimated
effect. Any discrepancies were resolved by a final consensus
amongst all reviewers.

RESULTS

Study selection
The electronic search strategy identified a total of
136 systematic reviews evaluating brain stimulation
interventions in persons with stroke. After removing
duplicates, 87 reviews met the abstract inclusion
criteria. The main reasons for exclusion of reviews included: non-systematic reviews, valuation of other
non-invasive brain stimulation (such as tDCS), and no
specific sub-group data of patients with stroke. Full
texts of these articles were retrieved, and all reviewers
performed the final selection. Further, one review was
identified from a manual search of bibliographies of
relevant articles. Overall, 12 systematic reviews with
a total of 9,117 subjects evaluating the effect of rTMS
on motor and functional outcomes; 3 reviews evaluated
(n = 1,916) (9, 24, 26) post-stroke depression outcomes,
and 2 reviews each evaluated aphasia (n = 157) (24, 33),
cognitive impairment (n = 301) (24, 34) and dysphagia
(n = 255) (25, 35).

Primary study design. Most primary studies included
were RCTs (192 of 235 studies), conducted between
January 1980 and December 2016. There was marked
variability amongst the studies with regard to the rTMS
protocols used. Nine of the 12 included systematic
reviews (21, 24–27, 32–35) performed meta-analyses,
and the other 3 provided only qualitative description
of findings due to heterogeneous data (9, 18, 23). Hao
et al. (24) conducted 4 sub-group meta-analyses: on
ADLs (2 RCTs, n = 183), motor function (4 RCTs,
n = 73), post-stroke depression (2 RCTs, n = 92) and
cognition (2 RCTs, n = 75). Similarly, Zhang et al.
(27) performed 6 sub-group meta-analyses on: effect
duration (38 RCTs, n = 979), stroke duration (16 RCTs,
n = 399), rTMS frequency (31 RCTs, n = 866), theta
burst stimulation (TBS) mode (9 RCTs, n = 125), lesion
location (27 RCTs, n = 750) and number of sessions (25
RCTs, n = not provided).

rTMS protocols in the included studies. The rTMS pro-
tocol applied to motor cortex varied amongst the studies:
with excitatory stimulation performed on the affected
hemisphere (with lesion) to increase the efficacy of re-
| Author, year | Domain | Number of studies and participants | Search date | Interventions | Outcome measures | Main findings |
|-------------|--------|-----------------------------------|-------------|---------------|-----------------|--------------|
| Graef et al. (21) 2016 | Motor | N = 11 RCTs, 199 participants | Search date: Up to Nov 2015 | rTMS: 20 min for 10 days, 1-50 Hz, AH and UH | UL motor function: FMA, WMFT, ARAT, BBT, JTHF, NHPT, MAL - motor improvement in hand function | No effect on any UL functions: SMD: 0.03, 95% CI: −0.03, 0.22, p = 0.08 |
| Mclntyre et al. (9) 2016 | PSD | N = 1 RCT, 1 pre-post study, 40 participants | Search date: Jan 1980 to June 2016 | rTMS: 1–10 Hz; 1,000–10,000 HDRS pulses; 10 sessions; 10–20 trains/session with 5–10 s trains; 100–110% RMT | Sham rTMS or none | Positive results in depression VERY LOW symptom reduction (% decrease in HDRS score range: 38–41.4%) |
| Ludemann- Podubecka et al. (23) 2015 | Motor | N = 7 RCTs, 871 participants | Search date: Up to June 2014 | rTMS over the UH: 1 Hz; 90–120% of effectiveness: RMT, 150–1,800 pulses ± motor difference between therapy exercises rTMS over the AH: 1–20 Hz; 80–130% RMT; 600–1,000 pulses; 1–20 days ± motor therapy exercises bilateral rTMS: 1 Hz rTMS over the UH ± iTBS over the AH; 90% RMT; 1,000 pulses | Sham rTMS or none | Positive effect for motor recovery of LOW affected hand Reasonable evidence for 10 Hz/10 sessions; largest positive effect by 20 Hz/10 sessions. Positive effect on hand function Inhibition showed better efficiencies after application of a single session rTMS. Facilitation showed better efficiencies after application of repeated rTMS sessions. |
| Kang et al. (32) 2016 | Motor | N = 12 RCTs, 343 participants | Search date: June 2015 to February 2016 | rTMS: 1–10 Hz: 90–130% Pinch force, Grip force, RMT; 200–1,800 pulses; 1–20 sessions | Elbow flexion torque, Knee extension torque | rTMS facilitated force production HIGH capabilities: ES: 0.66, 95% CI: 0.45, 0.86, p < 0.0001 |
| Salazar et al. (34) 2018 | Cognition | N = 10 RCTs, 266 participants | Search date: Up to Dec 2016 | HF-rTMS or LF-rTMS or iTBS or cTBS - Hemispatial neglect: 1 type of neuropsychological exercise + 1 type of clinical and cognitive assessment: MODERATE Vs. LOW 0.5–50 Hz, 80–90% RMT, 10–28 sessions lasting 10–20 min each, once or twice a day, during 2–5 weeks | Sham or none | Positive effects on hemispatial MODERATE neglect: SMD: −2.16, 95% CI: −3.00, −1.33, p < 0.0001 |
| Dionisio et al. (18) 2018 | Motor | N = 70 studies, 32 RCTs and 38 non-RCTs, 3,744 participants | Search date: 2005 to Aug 2016 | HF-rTMS or LF-rTMS or iTBS or cTBS - Multiple clinical and cognitive outcomes: ES: 0.44, 95% CI: 0.30, 0.56, p < 0.001 rTMS facilitated force production HIGH capabilities: ES: 0.66, 95% CI: 0.45, 0.86, p < 0.0001 | Sham or exercise | Significant improvements in VERY LOW Analytic outcomes: MRC, MAS, NIHSS, hand grip, Functional outcomes: FMA, WMFT, ARAT, BBT, JTHF, NHPT, 10MWT, PPT ADL: BI, MAL no significant increase: SMD: 15.92, LOW 95% CI: –2.11, 33.35, p = 0.084 no significant effect: SMD: 0.51, 95% CI: −0.99, 2.01, p = 0.51 no significant decrease: SMD: −0.12, 95% CI: –13.84, 13.59, p = 0.99 no significant effect: SMD: 1.87, 95% CI: –5.93, 9.68, p = 0.64 significant improvement: SMD: 19.8, p = 0.002 |
| Tao et al. (24) 2013 | Function | N = 19 RCTs, 588 participants | Search date: Up to April 2012 | LF vs HF-rTMS ± baseline treatment: ADL: BI = 5.0 to 50 Hz; 5 days to 4 weeks | Modified BI | rTMS facilitated force production HIGH capabilities: ES: 0.66, 95% CI: 0.45, 0.86, p < 0.0001 |
| Zhang et al. (27) 2017 | Motor | N = 34 RCT, 904 participants | Search date: up to Oct 2016 | Different protocol durations of rTMS from 1 to 24 days | grip force - key board tapping - movement accuracy - pinch and lift force - complex hand movement | Significant improvements in VERY LOW - both long (SMD: 0.49, 95% CI: 0.29, 0.68, p < 0.001) and short (SMD: 0.43, 95% CI: 0.30, 0.56, p < 0.001) term effects - acute stroke (SMD: 0.69, 95% CI: 0.41, 0.97, p < 0.001) rather than subacute (p < 0.002) or chronic (p = 0.048) - iTBS (SMD: 0.60, 95% CI: 0.10, 1.10, p = 0.018) rather than rTBS (p = 0.138) - subcortical lesions (SMD: 0.66, 95% CI: 0.36, 0.95, p < 0.001) rather than non-specified (p < 0.001) - 5 sessions of rTMS (SMD: 0.67, 95% CI: 0.41, 0.92, p < 0.001) rather than single (p < 0.001) or 10 sessions (p = 0.73) - Improvement in Picture naming LOW - Overall improvement in language assessments: SMD: 0.448, 95% CI: 0.23–0.66, p < 0.001 |
| Shah-Basak et al. (33) 2016 | Aphasia | N = 4 RCT, 4 non-RCTs, 143 participants | Search date: up to October 2014 | rTMS: 1–6 Hz; 10–11 days; different number of naming sessions | Secondary: multiple language assessment | All studies (p = 0.33) |
Repetitive transcranial magnetic stimulation in stroke

Table I. cont.

| Author, year | Domain | Number of studies and participants | Search date | Interventions | Outcome measures | Main findings | GRADE* |
|--------------|--------|-----------------------------------|-------------|---------------|-----------------|--------------|--------|
| Liao et al. (25) 2017 | Dysphagia | N = 6 RCT, 163 participants | Search date: up to March 2016 - Meta-analysis performed | rTMS over the AH, UH or bilateral - 1 to 5 Hz; 300–1,200 pulses per day; 1–2 weeks | - Dysphagia Grade - PAS - Standardized swallowing assessment | - Effective on unaffected and bilateral MODERATE hemispheres stimulation - Better result with HF-rTMS than LF-rTMS - Overall effect: SMD: 1.24, 95% CI: 0.67, 1.81, p<0.0001 |
| Shen et al. (26) 2017 | PSD | N = 22 RCTs, 1764 participants | Search date: Up to November 2016 - meta-analysis performed | rTMS: 0.2 to 15 Hz; 60–110% RMT, 20–30 trains; 1–10 s trains; 1,000–1,960 pulses/session; 7–28 sessions | - HDRS - Stroke severity, response rate, remission rate, MARDS | - rTMS improves HDRS, spindles, and ADL. - No effect on remission rate - Overall effect of rTMS on post-stroke depression: SMD: – 6.09, 95% CI: –7.74, –4.45, p<0.0001 |
| Pisegna et al. (35) 2015 | Dysphagia | N = 4 RCTs, 92 participants | Search date: up to July 2014 - meta-analysis performed | rTMS over the AH or UH, 1–50 Hz; RMT 90–120%; 1–20 blocks; 30–1,200 pulses; 1–10 days | - PAS - DOSS - FDS | Improvement in dysphagia: SMD: LOW 0.56, 95% CI: 0.04, 1.09, p = 0.03 |

*45-min conventional PT or OT, task-related exercises, CIMT, voluntary muscle contraction of the UL, fingers motor training. 31Hz rTMS on the UH vs 3, 5 and 10 Hz rTMS on the AH; 80–130% RMT; 150–1,800 pulses (5 RCTs) /cTBS on the UH vs iTBS on the AH; 80–90% RMT; 300–600 pulses (4 RCTs). Conventional rehabilitation treatment, visuospatial training, feedback training, visual scanning + motor training. Repetitive transcranial magnetic stimulation: 1 Hz rTMS over the UH or bilateral (36). Frequency of stimulations used by the studies ranged from 0.5 to 50 Hz at 60–130% resting motor threshold (RMT). Stimulating pulses also varied from 40 to 10,000. The total number of rTMS session ranged from 1 to 28, with duration ranging from 10 to 20 min. The control interventions varied, comparing sham rTMS alone or with some additional therapies (e.g. physiotherapy, occupational therapy, acupuncture, medications, etc.).

Outcomes evaluated. The outcomes evaluated across the included reviews focused on 5 main domains: motor, aphasia, depression, dysphagia and cognition. The outcome measures to objectively determine the possible effect of rTMS on both functional and non-functional outcomes differed amongst studies, including motor function (muscle strength/force, symptom management (spasticity, pain, etc.), ADLs; psychological outcomes, etc. The majority of primary studies within the included reviews evaluated clinical and functional motor outcomes, mainly upper limb function. Other primary outcomes assessed were mixed and depended on the impairment domain evaluated. (Table I). The study assessment points also varied: the majority tested the possible effect of rTMS during the intervention and immediately post-intervention; and few assessed the longer term impact.

Quality assessment of the included reviews

Two reviewers (CR, PH) rated the quality of each included review using the AMSTAR tool. The kappa level of agreement between both authors for AMSTAR assessment was 0.91. The overall mean AMSTAR methodological quality score for included systematic reviews was 7.3 and ranged from 2 to 10 out of 11. Two reviews were rated as “low-” quality (AMSTAR scores =0–4), 5 were rated “moderate-” quality (AMSTAR scores =5–8), and 5 “high-” quality (AMSTAR scores =9–11) (Table II).

All reviews, except 1 (25), had published an a priori protocol. All reviews, except 2 (18, 23), performed a comprehensive literature search of medical science databases. Two reviews (9, 22) did not include a grey literature search. All reviews, except 2 (18, 23), assessed the scientific quality of the primary studies using validated tools: 4 used PEDro, 3 used the Cochrane risk of bias tool, 1 review each used GRADE, Downs and Black tool, and the Revised CONSORT Statement. Only 2 reviews (24, 33) explicitly listed the excluded studies. None of the reviews stated the sources of funding for each of the included primary studies (Table II).
Effects of intervention

As mentioned above, the scope and measured outcomes amongst the included reviews varied. Overall quality of evidence for the use of rTMS was assessed using the GRADE assessment tool (Table III) and summary of impact of the rTMS on specific outcome domain categories are shown in Table IV. The existing best-evidence synthesis for rTMS for the management of post-stroke impairments based on outcomes is summarized below and in Table I.

Motor function

Six reviews ($n=138$ RCTs, 38 non-RCTs; 6,317 participants) evaluated various motor outcomes (18, 21, 23, 24, 27, 32). The overall findings suggest that there is “low-” to “moderate-” quality evidence for the beneficial effect of rTMS on any motor function evaluated. Graef et al. (21) investigated rTMS (inhibition over the unaffected hemisphere (UH) and facilitation over the affected hemisphere (AH)) combined with upper-limb training. The authors did not find any positive effect on hand motor recovery after inhibitory rTMS over the UH and bilateral rTMS, but were unable to recommend its routine use. Kang et al. (32) found that rTMS alone, or in combination with motor training, facilitated force

Table II. Quality assessment of included reviews

| Author, year | AMSTAR* Items |
|--------------|---------------|
|              | 1  2  3  4  5  6  7  8  9  10  11  Total score/11 |
| Graef et al. (21) 2016 | Yes  Yes  Yes  Yes  No  Yes  Yes  Yes  Yes  No  9 |
| McIntyre et al. (9) 2016 | Yes  NA  Yes  N  No  Yes  Yes  Yes  Yes  No  6 |
| Ludemann-Podubecka et al. (23) 2015 | Yes  NA  No  No  No  Yes  No  No  NA  No  2 |
| Kang et al. (32) 2016 | Yes  NA  Yes  Yes  No  Yes  Yes  Yes  Yes  No  8 |
| Salazar et al. (34) 2018 | Yes  Yes  Yes  Yes  No  Yes  Yes  Yes  Yes  NA  8 |
| Dionisio et al. (18) 2018 | Yes  NA  No  Yes  No  Yes  No  No  CA  No  3 |
| Hao et al. (24) 2013 | Yes  Yes  Yes  Yes  Yes  Yes  Yes  Yes  Yes  No  10 |
| Zhang et al. (27) 2017 | Yes  No  Yes  Yes  No  N  Yes  Yes  Yes  Yes  7 |
| Shah-Basak et al. (33) 2016 | Yes  NA  Yes  Yes  Yes  Yes  Yes  Yes  Yes  No  9 |
| Liao et al. (25) 2017 | Yes  Yes  Yes  Yes  No  Yes  Yes  Yes  Yes  NA  7 |
| Shen et al. (26) 2017 | Yes  Yes  Yes  Yes  No  Yes  Yes  Yes  Yes  No  9 |
| Pisegna et al. (35) 2015 | Yes  Yes  Yes  Yes  NA  Yes  Yes  Yes  Yes  No  9 |

AMSTAR: Assessment of Multiple Systematic Reviews; CA: can’t answer; NA: not applicable.

Table III. GRADE* assessment of included studies

| GRADE | Inconsistency | Interval overlaps | Direction of effect | Imprecision | Sample size | Included studies |
|-------|---------------|-------------------|---------------------|-------------|-------------|-----------------|
| GRADE |              |                   |                     |             |             |                 |
| Graef et al. (21), 2016 | Yes | Substantial overlap | No | Low | Intermediate | Moderate |
| McIntyre et al. (9), 2016 | No meta-analysis performed as heterogeneous study | | | | | |
| Ludemann-Podubecka et al. (23), 2015 | No meta-analysis performed as heterogeneous study | | | | | |
| Kang et al. (32), 2016 | No | Substantial overlap | Yes | Low | Intermediate | Moderate |
| Salazar et al. (34), 2018 | Yes | Substantial overlap | Yes | High | Intermediate | Moderate |
| Dionisio et al. (18), 2018 | No meta-analysis performed as heterogeneous study | | | | | |
| Hao et al. (24), 2013 | Yes | Some overlap | No | High | Intermediate | Moderate |
| Zhang et al. (27), 2017 | Yes | Some overlap | Yes | Low | Intermediate | Moderate |
| Shah-Basak et al. (33), 2016 | Yes | Substantial overlap | Yes | Moderate | Low | Small |
| Liao et al. (25), 2017 | Yes | Substantial overlap | Yes | High | Moderate | Small |
| Shen et al. (36), 2017 | Yes | Some overlap | Yes | High | Moderate | Small |
| Pisegna et al. (35), 2015 | Yes | Substantial overlap | No | Low | Low | Small |

*GRADE: Grade of Recommendations; Assessment; Development, and Evaluation Working Group grades of evidence.
production capabilities (effect size (ES) = 0.66, 95% CI = 0.45–0.86, p < 0.0001). Dionisio et al. (18) also reported significant improvements in functional and clinical capabilities after rTMS (inhibition over the UH and facilitation over the AH). Similarly, Zhang et al. (27) found significant improvements in upper limb function after rTMS, both for short-term effect (SMD = 0.43, 95% CI = 0.30–0.56, p < 0.001) and long-term effect (SMD = 0.49, 95% CI = –0.29 to 0.68, p < 0.001). In contrast, Hao et al. (24) did not find any significant improvement in functional scores after rTMS (inhibition over the UH and facilitation over the AH) on functional outcomes (Barthel Index (BI), SMD = 15.92, 95% CI = –2.11 to 3.95, p = 0.084) or on other motor function (SMD = 0.51, 95% CI = –0.99 to 2.01, p = 0.51).

Aphasia. Two reviews (n = 5 RCTs, 4 non-RCTs; 157 participants) evaluated the efficacy of rTMS on various aphasia outcomes (24, 33). The overall findings suggest some beneficial effect of rTMS on patients with post-stroke aphasia. Hao et al. (24) (n = 1 RCT, 14 participants) reported a significant improvement on the Aachen Aphasia Test total score (SMD = 19.8, p = 0.002) after inhibitory rTMS over the UH. Similarly, Shah-Basak et al. (33) in another review found overall improvement in language assessment (SMD = 0.448, 95% CI = 0.23 to 0.66, p < 0.001) after rTMS applied over non-lesion hemisphere or bilateral.

Post-stroke depression. Three reviews (n = 26 RCTs, one non-RCTs; 1,916 participants) evaluated the effectiveness of rTMS on depression outcomes, using the Hamilton Depression Rating Scale (HDRS) (9, 24, 26). Overall findings indicate, “low-” quality evidence for beneficial effect of rTMS on post-stroke depression outcomes. McIntyre et al. (9) (n = 1 RCT, 40 participants) found limited benefit on depression in the short-term after rTMS (inhibition over the UH and facilitation over the AH); whereas Hao et al. (24) (n = 2 RCTs, 92 participants) did not find any decrease in the HDRS score (bilateral low frequency rTMS) (SMD = –0.12, 95% CI = –13.84 to 13.59, p = 0.99). Shen et al. (26) found improvement in the PSD (HDRS, mean difference (MD) = –6.09, p < 0.001); response rates (odds ratio (OR) = 3.46, p < 0.001); remission rates (OR 0.99, p < 0.001); National Institutes of Health Stroke Scale, MD = –2.74, p < 0.001).

Dysphagia. Two reviews (25, 35) (n = 10 RCTs, 255 participants) evaluated efficacy of rTMS on various dysphagia outcomes in persons following stroke. The overall findings suggest that there is “moderate-” quality evidence for the beneficial effect of rTMS on patients with post-stroke dysphagia. Liao et al. (25) reported a positive effect of rTMS (over the UH and bilateral) on post-stroke dysphagia symptoms (SMD = 1.24, 95% CI = 0.67–1.81, p < 0.0001). Similar findings of a beneficial effect of rTMS on dysphagia outcomes in the shorter term were reported in another review (SMD 0.56, 95% CI = –0.04–1.09, p = 0.03) (35).

Cognition. Two reviews (n = 12 RCTs, 301 participants) evaluated the effects of rTMS on cognitive outcomes in person with stroke (24, 34). The overall findings indicate a “moderate-” quality evidence for beneficial effect of rTMS on cognitive function (such as hemispatial neglect, mental state, etc.). Salazar et al. (34) found positive effects of rTMS combined with other cognitive rehabilitation interventions in the line bisection test and the modified BI (SMD = –2.16, 95% CI = –3.00 to –1.33, p < 0.0001). Hao et al. (24) (n = 2 RCTs, 75 participants) showed that low-frequency rTMS did not have any significant effect on MMSE scores (SMD = 1.87, 95% CI = –5.93 to 9.68, p = 0.64).

This review systematically analysed evidence from published systematic reviews to date, for the effectiveness of rTMS on motor and non-motor functions in persons following stroke. The findings indicate that, although rTMS is widely trialled in this population, there is still lack of high-quality evidence for its routine use in clinical practice. The overall findings of this review of the use of rTMS in persons with stroke suggest:

• “Moderate-” quality of evidence for improved post-stroke dysphagia and to reduce hemineglect.
• “Low-” to “moderate-” quality of evidence for enhanced motor function (upper limb function, ADLs).
• “Low-” quality of evidence for reduction in post-stroke depression and aphasia.

There was heterogeneity amongst the included reviews, even in those evaluating similar outcomes. The methodological quality of the included systematic reviews varied, with only 5 out of 12 rated as of “high” methodological quality (AMSTAR score) (30). Likewise, evidence for the use of rTMS targeting different stroke-related outcomes in the included reviews was diverse. This is mainly due to variation in operational procedures of rTMS (duration, intensity, etc.), outcome measurement tools, control intervention protocols and length of follow-up. Therefore, pooling data for quantitative analyses was not possible, and a best-evidence synthesis was described using qualitative analyses. For some outcomes evaluated, there were few primary studies within the included reviews, most with significant methodological limitations. Overall evidence for some of the studies was downgraded from actual evidence reported by authors, due to imprecision and inconsistency of findings, use of different outcome measures.
and inclusion of non-RCTs with poor methodology quality, precluding meta-analysis.

To our knowledge, this is first review to systematically appraise published systematic reviews to evaluate the effectiveness of rTMS for various stroke-related impairments in motor and non-motor domains. This approach of synthesizing findings of systematic reviews enables the comparison of results from multiple reviews, thereby providing a comprehensive evidence-based summary on evident outcomes. Recently, Leon Ruiz et al. published a narrative review of current evidence of rTMS in stroke neurorehabilitation, based on clinical practice guidelines and published recommendations (37). In comparison to our findings, the authors of this review reported beneficial effect of rTMS in treating stroke complications, including motor disorders, aphasia, dysarthria, oropharyngeal dysphagia, depression, and perceptual-cognitive deficits. However, consistent with our findings, these authors suggested further well-designed clinical trials with larger sample size with a higher level of evidence for proper implementation of rTMS use in stroke (37). Other published clinical practice guidelines on rTMS do not report recommendations specific to post-stroke population (38, 39).

The mechanisms underlying the effects of rTMS applied over the motor cortex are described in the literature (40). Non-invasive brain stimulation, such as rTMS over the motor cortex, induces changes, not only in the target motor area, but also in many cortico-subcortical and spinal structures, resulting in excessive interhemispheric inhibition from the non-lesional hemisphere after stroke (38, 39). This has led to exploration of possible therapeutic effects of rTMS with diverse protocols (facilitation, inhibition or combined), reflecting the range and number of studies identified in this review. Despite established guidelines (38, 39), standardized protocols are yet to be employed, with individual studies using varying range of protocols (rTMS frequency stimulations range 0.5–50 Hz, stimulating pulses 40–10,000, rTMS sessions 1–28, with duration ranging from 10 to 20 min) and characteristics of stimulation protocol (number of sessions, duration, intensity). Further, the outcome measures used and assessment time-points also differed. The measures used were specific to upper-limb function and ADLs. Objective methods, such as functional magnetic resonance imaging (fMRI), neurophysiology, etc. were rarely used, despite their higher accuracy than clinical measures regarding subtle changes. The characteristics of participants were heterogeneous amongst the studies regarding the characteristics of stroke (type, lesion location and area, time since stroke, other comorbidities, age, etc.), which may have resulted in variability in findings. Further research is required into the confounding effects of adjunct therapies, including routine rehabilitation program, coupled with rTMS intervention.

**Study limitations**

Some limitations in methodology and the completeness of retrieved literature must be considered. Despite the comprehensive search employed, this review encompassed published literature written in English in specific health science databases, and only the bibliography of relevant articles was scrutinized. This may have introduced a selection and reference bias. However, extensive comprehensive searching, using broad search terms in most prominent databases, was used, and experts and prominent stroke-related organizations’ websites and the websites of experts and of prominent stroke-related organizations were explored to identify relevant studies. Widely used validated tools to assess methodology (AMSTAR) and quality of evidence (GRADE) of included studies were used. The accuracy of assessor’s assessments cannot be guaranteed; however, the selection of studies and quality assessments were independently performed by 3 authors, and further group consensus was achieved. Despite significant heterogeneity among the included reviews, with high variability in rTMS protocols and number of participants, we were able to categorize the effect of intervention on only 5 domains (motor function, aphasia, dysphagia, depression, cognition). These issues limit the generalizability of our findings. It was not possible to evaluate safety related to rTMS, as report of adverse events in the included reviews was incomplete or missing. The associated costs and/or economic benefit of rTMS were not reported in any review. Many included reviews had search dates up to 3 years prior to our systematic review, so we may have missed some recent studies which were not included in these review. Hence, the findings of this review should be interpreted with caution.

**Conclusion**

The management of persons following stroke is complex and challenging. Non-invasive brain stimulation techniques, including rTMS, are widely used, despite a lack of high-quality evidence for improved motor and non-motor functions in stroke survivors. Some positive effect of rTMS were noted for outcomes (dysphagia, hemineglect, aphasia and depression), but its routine use cannot yet be recommended. Further studies in larger cohorts with robust methodology are required for differential roles of various rTMS protocols and longer-term after-effects of rTMS in stroke. Future studies should take into account patient characteristics,
rTMS stimulation parameters, stroke type and duration since stroke, due to the significance of the critical period after stroke for neuropsychological recovery.

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