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Hao Z, Wang D, Zeng Y, Liu M

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[Intervention Review]

Repetitive transcranial magnetic stimulation for improving function after stroke

Zilong Hao¹, Deren Wang¹, Yan Zeng², Ming Liu¹

¹Department of Neurology, West China Hospital, Sichuan University, Chengdu, China. ²Neurobiological Laboratory Centre, West China Hospital, Sichuan University, Chengdu, China

Contact address: Ming Liu, Department of Neurology, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China. wylmh@hotmail.com.

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ABSTRACT

Background

It had been assumed that suppressing the undamaged contralesional motor cortex by repetitive low-frequency transcranial magnetic stimulation (rTMS) or increasing the excitability of the damaged hemisphere cortex by high-frequency rTMS will promote function recovery after stroke.

Objectives

To assess the efficacy and safety of rTMS for improving function in people with stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (April 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 4), the Chinese Stroke Trials Register (April 2012), MEDLINE (1950 to May 2012), EMBASE (1980 to May 2012), Science Citation Index (1981 to April 2012), Conference Proceedings Citation Index-Science (1990 to April 2012), CINAHL (1982 to May 2012), AMED (1985 to May 2012), PEDro (April 2012), REHABDATA (April 2012) and CIRRIE Database of International Rehabilitation Research (April 2012). In addition, we searched five Chinese databases, ongoing trials registers and relevant reference lists.

Selection criteria

We included randomised controlled trials comparing rTMS therapy with sham therapy or no therapy. We excluded trials that reported only laboratory parameters.

Data collection and analysis

Two review authors independently selected trials, assessed trial quality and extracted the data. We resolved disagreements by discussion.

Main results

We included 19 trials involving a total of 588 participants in this review. Two heterogeneous trials with a total of 183 participants showed that rTMS treatment was not associated with a significant increase in the Barthel Index score (mean difference (MD) 15.92, 95% CI -2.11 to 33.95). Four trials with a total of 73 participants were not found to have a statistically significant effect on motor

function (standardised mean difference (SMD) 0.51, 95% CI -0.99 to 2.01). Subgroup analyses of different stimulation frequencies or duration of illness also showed no significant difference. Few mild adverse events were observed in the rTMS groups, with the most common events being transient or mild headaches (2.4%, 8/327) and local discomfort at the site of the stimulation.

Authors' conclusions

Current evidence does not support the routine use of rTMS for the treatment of stroke. Further trials with larger sample sizes are needed to determine a suitable rTMS protocol and the long-term functional outcome.

PLAIN LANGUAGE SUMMARY

Magnetic brain stimulation for improving people's functional ability after stroke

The human brain has two hemispheres. For people who have had a stroke, activity in the affected hemisphere is disrupted not only by the damage caused by the stroke itself, but also by the reaction of the unaffected hemisphere, which tries to limit the damage caused by the stroke. This limiting effect, while beneficial in the initial stage after stroke, may subsequently become detrimental as it interferes with the brain's capacity to recover functional ability. Repetitive transcranial magnetic stimulation (rTMS) is a method of non-invasive brain stimulation that can help the affected hemisphere to repair the damage of the stroke, while decreasing the limiting effect on recovery caused by undamaged hemisphere. rTMS has been investigated in the treatment of many conditions, including depression, tinnitus and movement disorders. The aim of this review was to assess randomised controlled trials of rTMS on functional recovery in patients with stroke. We included 19 trials with a total of 588 patients in the review. We found that rTMS treatment was not associated with improved activities of daily living nor had a statistically significant effect on motor function. The current evidence is not yet sufficient to support the routine use of rTMS for the treatment of stroke.

BACKGROUND

Description of the condition

Stroke is the second most common cause of death and the leading cause of adult disability in the world. As a result of the ageing population, the burden of stroke will increase in the next 20 years (Donnan 2008). At present, there are limited effective interventions for patients with acute stroke (Langhorne 2009). Consequently, the management of most patients with stroke remains primarily focused on secondary prevention and rehabilitation (European Stroke Organisation 2009). Any intervention that enables patients to recover more rapidly or gain functional independence would have major benefits for patients and their families. In addition, brain recovery and rehabilitation will also be a prioritised field in future stroke research (Hachinski 2010).

Description of the intervention

Repetitive transcranial magnetic stimulation (rTMS) is a method of non-invasive brain stimulation that affects the cerebral cortex (Hummel 2006). Fast-oscillating magnetic fields, created by

a strong electric current, penetrate human tissue painlessly and result in electrical currents in the brain that can modulate cortical excitability by decreasing or increasing it (depending on parameters of stimulation) (Fregni 2008; Rossini 2007) and potentially improve functional outcomes.

How the intervention might work

The idea of using rTMS to improve motor function in patients with stroke is based on interhemispheric inhibition, which means the contralesional hemisphere might inhibit surviving cortical motor systems by transcallosal inhibition (Murae 2004; Ward 2004). In people with stroke, activity in the affected hemisphere is disrupted not only by the damage caused by the stroke itself but also by inhibition from the unaffected hemisphere, which further reduces the excitability of the affected hemisphere. Consequently, it is assumed that a possible target for rTMS is the contralesional motor cortex or damaged hemisphere cortex, which means that suppressing the undamaged contralesional motor cortex by low-frequency rTMS or increasing the excitability of the damaged hemisphere cortex by high-frequency rTMS will promote motor recovery after stroke (Hummel 2006; Ward 2004). High-frequency

rTMS refers to stimulus rates of more than 1 Hz, and low-frequency rTMS refers to stimulus rates of 1 Hz or less (Rossi 2009).

Why it is important to do this review

The use of this technique has been investigated in the treatment of many conditions, including depression (Rodriguez-Martin 2002), tinnitus (Meng 2009), movement disorders (Edwards 2008) and obsessive compulsive disorder (Rodriguez-Martin 2003). Although there are a few published studies of the clinical efficacy of rTMS on motor recovery in stroke patients (Ameli 2009; Khedr 2009; Kirton 2008; Mansur 2005; Takeuchi 2009; Yozbatiran 2009), the potential therapeutic effect of rTMS has been controversial. The aim of this review was to assess systematically all the randomised controlled trials of rTMS on functional recovery in patients with stroke to provide the best available evidence.

OBJECTIVES

To assess the efficacy and safety of rTMS for improving function after stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We include randomised controlled trials (RCTs) in which the authors compare rTMS therapy with sham therapy or no therapy. We excluded trials in which the authors report only laboratory parameters.

Types of participants

We include studies with participants of any age or sex after stroke, regardless of the duration of illness or severity of the initial impairment. The clinical definition of stroke was that of the World Health Organization criteria (Stroke 1989), excluding stroke mimics by computerised tomography (CT) or magnetic resonance imaging (MRI) scan.

Types of interventions

We include all trials that evaluated rTMS therapy in patients with stroke, regardless of ipsilateral or bilateral stimulation, frequency, age or duration of illness. The control interventions were sham treatment or other conventional treatment.

We investigated the following comparisons:

1. rTMS only compared with sham treatment;
2. rTMS add-on baseline treatment compared with sham treatment add-on baseline treatment;
3. rTMS add-on baseline treatment compared with baseline treatment alone.

Types of outcome measures

We assessed outcomes at the end of treatment period and scheduled follow-up.

Primary outcomes

Activities of daily living, such as the Barthel index, the Functional Independence Measure, and the modified Rankin Scale.

Secondary outcomes

1. Motor function: upper limb function (e.g. Motor Assessment Scale (MAS), Action Research Arm Test, Nine-Hole Peg Test, etc); lower limb function (e.g. changes in stride length (centimetres) or speed (time taken to walk a specific distance), Timed Up and Go Test, Rivermead Motor Assessment Scale, etc); Global motor function (e.g. MAS, Rivermead Motor Assessment Scale, etc).
2. Death or disability.
3. Any other impairment improvement (e.g. visual, perceptual, depression, cognition, etc).
4. Adverse outcome (e.g. seizure, headache, dizziness, etc).

Search methods for identification of studies

See the 'Specialized register' section in the [Cochrane Stroke Group](#) module. We searched for trials in all languages and arranged translation of relevant reports published in languages other than English and Chinese.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor in April 2012. In addition, and in collaboration with the Cochrane Stroke Group Trials Search Co-ordinator, we searched the following bibliographic databases:

- the Chinese Stroke Trials Register (April 2012);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 4);
- MEDLINE (1950 to May 2012) ([Appendix 1](#));
- EMBASE (1980 to May 2012) ([Appendix 2](#));
- ISI Science Citation Index (1981 to April 2012);
- CINAHL (1982 to May 2012) ([Appendix 3](#));

- AMED (the Allied and Complementary Medicine Database (1985 to May 2012) ([Appendix 4](#));
- PEDro (Physiotherapy Evidence Database) (www.pedro.org.au/) (April 2012);
- REHABDATA (www.naric.com/research/rehab/default.cfm) (April 2012);
- CIRRIE Database of International Rehabilitation Research (<http://cirrie.buffalo.edu/index.html>) (April 2012);
- The China Biological Medicine Database (CBM) (1978 to April 2012);
- The Chinese National Knowledge Infrastructure (CNKI) (1979 to April 2012);
- Chinese Science and Technique Journals Database (VIP) (1989 to April 2012);
- Wanfang Data (www.wanfangdata.com/) (1984 to April 2012).

We also searched the following international trials registers in April 2012:

- ClinicalTrials.gov (www.clinicaltrials.gov/);
- Current Controlled Trials (www.controlled-trials.com/);
- Stroke Trials Registry (www.strokecenter.org/trials/).

Searching other resources

In an effort to identify further published, unpublished and ongoing studies, we searched databases of conference abstracts: Conference Proceedings Citation Index Science (CPCI-S) and China Medical Academic Conferences (CMAC 1995 to present) in CMCC (Chinese Medical Current Contents) (April 2012), and all reference lists of retrieved articles.

Data collection and analysis

Selection of studies

Two review authors (ZH and DW) independently scanned the titles, abstracts and keywords of records identified from the electronic searches and excluded obviously irrelevant citations. We obtained the full text of the remaining studies and the same two authors selected studies for inclusion based on the criteria outlined previously. We resolved any disagreements through discussion with a third author (ML).

Data extraction and management

Two review authors (ZH and DW) independently extracted details of patient characteristics, methods, interventions and outcomes by using a data extraction form. We resolved disagreements through discussion with a third author (YZ). For dichotomous outcomes we extracted the number of participants experiencing the event

and the total number of participants in each arm of the trial. For continuous outcomes we extracted the mean value and standard deviation for the changes in each arm of the trial along with the total number in each group.

Assessment of risk of bias in included studies

We assessed the methodological quality of selected studies as described in the Cochrane Handbook for Systematic Reviews of Interventions ([Cochrane Handbook](#)). We created a 'Risk of bias' table and included a description and a judgement (low risk of bias, high risk of bias, or unclear risk of bias) for the following domains for each of the included studies:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective reporting;
7. other sources of bias.

Two review authors independently performed quality assessment; we resolved any disagreements between authors arising at any stage through discussion or with a third author.

Measures of treatment effect

We expressed results for dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI), and expressed results for continuous outcomes as mean difference (MD) if the same scale for each trial was available, or standardised mean difference (SMD) if different scales were used. For continuous outcomes, we intended to compare the change scores between groups after treatment and at the end of the follow-up period.

Unit of analysis issues

For studies with non-standard designs (e.g. cross-over trials, cluster-randomised trials), we planned to manage the data according to the [Cochrane Handbook](#). For example, if we had found any cross-over trials, we would only have analysed the data from the first period.

Dealing with missing data

If data were missing, we contacted the investigators for additional information. If some data remained unavailable, we considered both best-case and worst-case scenarios.

Assessment of heterogeneity

We determined heterogeneity by using the I^2 statistic. We considered I^2 greater than 50% to be substantial heterogeneity ([Higgins 2003](#)).

Assessment of reporting biases

We used the funnel plot method (Egger 1997).

Data synthesis

We performed statistical analysis using RevMan 5.1 (RevMan 2013) and performed all analyses in accordance with the intention-to-treat method. We reported the results as RRs with 95% CIs for dichotomous data and as MDs or SMDs with 95% CIs for continuous data. We used a random-effects model to combine individual results. If there were no suitable studies, we planned to provide a narrative summary of the study results.

Subgroup analysis and investigation of heterogeneity

We planned a priori subgroup analyses based on:

1. stroke type: ischaemic stroke versus intracranial haemorrhage;
2. ipsilateral or bilateral stimulation;
3. different frequency (low frequency or high frequency);
4. duration of illness;
5. severity of initial impairment;
6. stimulus parameters.

Sensitivity analysis

We planned to perform sensitivity analyses by:

1. excluding studies with inadequate concealment of allocation;
2. excluding studies in which outcome evaluation was not blinded;
3. excluding studies in which loss to follow-up was not reported or was greater than 10%;
4. re-analysing the data by removing studies with nonstandard designs if we included these studies;
5. re-analysing the data by removing studies with assumed values to replace missing data.

RESULTS

Description of studies

Results of the search

After screening 2431 titles and abstracts, we retained 60 studies for further assessment. We included 19 trials involving a total of 588 participants in the review (Avenanti 2012; Barwood 2011a; Chen 2005; Du 2005; Fregni 2006; Jin 2002; Jorge 2004; Khedr 2005a;

Khedr 2009a; Khedr 2010; Kirton 2007; Koch 2012; Liepert 2007; Malcolm 2006; Mansur 2005; Pomeroy 2006; Takeuchi 2008; Wang 2012; Weiduschat 2011) (see Characteristics of included studies). We excluded 34 studies (Ackerley 2010; Acket 2011; Barwood 2011; Boyd 2010; Chang 2010; Conforto 2010; Conforto 2011; Cotelli 2011; Davis 2007; Fridman 2002; Hirayama 2006; Joen 2008; Jorge 2008; Kakuda 2011; Kate 2010; Khedr 2005; Kim 2006; Kisten 2004; Lefaucheur 2004; Linsdell 2010; Meehan 2011; Nowak 2008; Nyffeler 2009; Ravindran 2003; Rektorova 2005; Routhier 2010; Sedlackova 2005; Talelli 2007a; Talelli 2007b; Trettiluxana 2009; Wang 2010; Weiduschat 2009; Yoo 2008; Yoon 2010) (see Characteristics of excluded studies). We identified and included six ongoing trials (Ackerley 2010a; ContraStim 2010; Humphreys 2010; Leker 2008; NINDS 2006; Stinear 2006) (see Characteristics of ongoing studies).

Two trials used a cross-over design with random allocation to the order of treatment sequences (Liepert 2007; Mansur 2005). However, we could not obtain outcome data from the first period of these studies, so the data for these trials could not be pooled together with the data from other studies.

One trial was awaiting classification because it was completed but no data were available.

Included studies

Characteristics of participants in included studies

The 19 included trials involved 588 participants (Avenanti 2012; Barwood 2011a; Chen 2005; Du 2005; Fregni 2006; Jin 2002; Jorge 2004; Khedr 2005a; Khedr 2009a; Khedr 2010; Kirton 2007; Koch 2012; Liepert 2007; Malcolm 2006; Mansur 2005; Pomeroy 2006; Takeuchi 2008; Wang 2012; Weiduschat 2011). One trial included paediatric stroke (10 participants), with a mean age of 13.25 years (Kirton 2007). The mean age of participants in the remaining 18 trials ranged from 53.3 to 74.8 years. The proportion of men was 30% to 80% among these trials. The time between stroke and recruitment varied from four hours to six years. Eight trials included participants with stroke within 30 days of symptom onset (Jin 2002; Khedr 2005a; Khedr 2009a; Khedr 2010; Koch 2012; Liepert 2007; Pomeroy 2006; Weiduschat 2011), and 10 trials included participants with stroke from more than one month to six years of symptom onset (Avenanti 2012; Barwood 2011a; Chen 2005; Fregni 2006; Jorge 2004; Kirton 2007; Malcolm 2006; Mansur 2005; Takeuchi 2008; Wang 2012). One trial did not report the duration of illness (Du 2005). All participants had a CT or MRI scan before treatment. People with severe medical comorbidity or at risk of epilepsy were excluded from each trial.

Interventions in included studies

See the [Characteristics of included studies](#) table for details of the interventions. Trials were categorised into comparisons of: (1) repetitive transcranial magnetic stimulation (rTMS) compared with sham treatment ([Barwood 2011a](#); [Fregni 2006](#); [Jorge 2004](#); [Khedr 2005a](#); [Khedr 2009a](#); [Khedr 2010](#); [Kirton 2007](#); [Koch 2012](#); [Liepert 2007](#); [Mansur 2005](#); [Pomeroy 2006](#)); (2) rTMS add-on baseline treatment compared with sham treatment add-on baseline treatment ([Avenanti 2012](#); [Malcolm 2006](#); [Takeuchi 2008](#); [Wang 2012](#); [Weiduschat 2011](#)); (3) rTMS add-on baseline treatment compared with baseline treatment alone ([Chen 2005](#); [Du 2005](#); [Jin 2002](#)). The frequency of rTMS ranged from 0.5 Hz to 50 Hz. The duration of treatment varied from 10 minutes to four weeks.

Outcome measures of included studies

The included trials used a large number of heterogeneous outcome measures. Five trials reported activities of daily living in survivors ([Du 2005](#); [Jin 2002](#); [Khedr 2005a](#); [Khedr 2009a](#); [Khedr 2010](#)). Eight trials reported motor function of affected extremities ([Avenanti 2012](#); [Fregni 2006](#); [Khedr 2009a](#); [Liepert 2007](#); [Malcolm 2006](#); [Mansur 2005](#); [Pomeroy 2006](#); [Takeuchi 2008](#)). Other reported outcome measures included depression ([Chen 2005](#); [Du 2005](#); [Jorge 2004](#)), cognitive function ([Fregni 2006](#)), poststroke aphasia ([Weiduschat 2011](#)) and neglect ([Koch 2012](#)). The durations of follow-up were: three months in two trials ([Avenanti 2012](#); [Khedr 2009a](#)), six months in one trial ([Malcolm 2006](#)) and one year in another trial ([Khedr 2010](#)). Most included trials evaluated the outcome at the end of treatment period or within one month.

Excluded studies

We excluded 34 of the 60 trials we identified ([Ackerley 2010](#); [Acket 2011](#); [Barwood 2011](#); [Boyd 2010](#); [Chang 2010](#); [Conforto 2010](#); [Conforto 2011](#); [Cotelli 2011](#); [Davis 2007](#); [Fridman 2002](#); [Hirayama 2006](#); [Joel 2008](#); [Jorge 2008](#); [Kakuda 2011](#); [Kate 2010](#); [Khedr 2005](#); [Kim 2006](#); [Kisten 2004](#); [Lefaucheur 2004](#); [Linsdell 2010](#); [Meehan 2011](#); [Nowak 2008](#); [Nyffeler 2009](#); [Ravindran 2003](#); [Rektorova 2005](#); [Routhier 2010](#); [Sedlackova 2005](#); [Talelli 2007a](#); [Talelli 2007b](#); [Tretriluxana 2009](#); [Wang 2010](#); [Weiduschat 2009](#); [Yoo 2008](#); [Yoon 2010](#)). We excluded these trials for various reasons: non-RCT ([Ackerley 2010](#); [Hirayama 2006](#); [Kakuda 2011](#); [Nyffeler 2009](#); [Talelli 2007a](#)) or pseudo-RCT ([Chang 2010](#); [Khedr 2005](#); [Kim 2006](#); [Meehan 2011](#)); the participants ([Jorge 2008](#); [Lefaucheur 2004](#); [Rektorova 2005](#)) or outcome measurements ([Barwood 2011](#); [Nowak 2008](#)) or interventions ([Ravindran 2003](#)) did not meet the inclusion criteria, or the trials were confounded ([Cotelli 2011](#)). The remaining 18 excluded studies were only available as meeting abstracts that did not contain enough information to evaluate them. We therefore plan to re-evaluate them for the next version of this review ([Acket 2011](#); [Boyd 2010](#);

[Conforto 2010](#); [Conforto 2011](#); [Davis 2007](#); [Fridman 2002](#); [Joel 2008](#); [Kate 2010](#); [Kisten 2004](#); [Linsdell 2010](#); [Routhier 2010](#); [Sedlackova 2005](#); [Talelli 2007b](#); [Tretriluxana 2009](#); [Wang 2010](#); [Weiduschat 2009](#); [Yoo 2008](#); [Yoon 2010](#)).

Risk of bias in included studies

Allocation

Two trials allocated participants by using a computer random generator ([Avenanti 2012](#); [Pomeroy 2006](#)), and two trials reported the drawing of lots to divide the treatment and control groups ([Chen 2005](#); [Du 2005](#)). In one trial, the patient whose hospital identification number had the lowest final digit (or lowest penultimate digit, if the final digits of the two patients were the same) was assigned to rTMS treatment, the other to sham ([Kirton 2007](#)). The other included trials only reported 'randomly allocating' participants but the method of randomisation was not described ([Barwood 2011a](#); [Fregni 2006](#); [Jin 2002](#); [Jorge 2004](#); [Khedr 2005a](#); [Khedr 2009a](#); [Khedr 2010](#); [Koch 2012](#); [Liepert 2007](#); [Malcolm 2006](#); [Mansur 2005](#); [Takeuchi 2008](#); [Wang 2012](#); [Weiduschat 2011](#)).

Five trials adequately concealed the randomisation sequence by using sealed envelopes ([Khedr 2009a](#); [Khedr 2010](#); [Pomeroy 2006](#); [Wang 2012](#); [Weiduschat 2011](#)). The concealment of the other trials was unclear.

Blinding

Sixteen trials used sham stimulation as the control group, but the success of blinding was not recorded. In these trials, three trials reported that participants, investigators and assessors were blinded ([Fregni 2006](#); [Koch 2012](#); [Weiduschat 2011](#)), 10 trials reported participants and assessors were blinded ([Avenanti 2012](#); [Jorge 2004](#); [Khedr 2005a](#); [Khedr 2009a](#); [Khedr 2010](#); [Kirton 2007](#); [Liepert 2007](#); [Malcolm 2006](#); [Pomeroy 2006](#); [Wang 2012](#)), and three trials reported participants were blinded ([Barwood 2011a](#); [Mansur 2005](#); [Takeuchi 2008](#)). Three trials used regular treatments as the control group: of these, one trial reported assessors were blinded ([Chen 2005](#)) and two trials did not report the method of blinding ([Du 2005](#); [Jin 2002](#)).

Incomplete outcome data

None of included trials stated that an intention-to-treat analysis had been performed. No exclusions after randomisation or losses to follow-up were reported in 13 trials ([Avenanti 2012](#); [Barwood 2011a](#); [Chen 2005](#); [Du 2005](#); [Fregni 2006](#); [Jin 2002](#); [Jorge 2004](#); [Khedr 2005a](#); [Khedr 2009a](#); [Kirton 2007](#); [Liepert 2007](#); [Malcolm 2006](#); [Takeuchi 2008](#)) for the overall outcome. In one trial, 10 of the 48 participants did not complete the follow-up. In another trial, three participants were lost to follow-up ([Weiduschat 2011](#)).

Four trials reported that participants were excluded after randomisation (Koch 2012; Mansur 2005; Pomeroy 2006; Wang 2012) (see [Characteristics of included studies](#)).

Selective reporting

There was insufficient information for us to make a judgement on selective reporting.

Other potential sources of bias

The funnel plots with the greatest number of trials investigating improvement of motor function showed a slightly asymmetrical funnel distribution, which indicated that there was likely to have been some publication bias ([Figure 1](#)).

Figure 1. Funnel plot of comparison: 1 rTMS compared with control, outcome: 1.2 Motor function.

Please see summary figures of risk of bias ([Figure 2](#); [Figure 3](#)).

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

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Avenanti 2012	+	?	+	+	+	?	?
Barwood 2011a	?	?	+	?	?	?	?
Chen 2005	+	?	-	+	+	?	?
Du 2005	+	?	-	?	+	?	?
Fregni 2006	?	?	+	+	+	?	?
Jin 2002	?	?	?	?	+	?	?
Jorge 2004	?	?	+	+	+	?	?
Khedr 2005a	?	?	+	+	+	?	?
Khedr 2009a	?	+	+	+	?	?	?
Khedr 2010	?	+	+	+	-	?	?
Kirton 2007	+	?	+	+	+	?	?
Koch 2012	?	?	+	+	+	?	?
Liepert 2007	?	?	+	+	+	?	?
Malcolm 2006	?	?	+	+	+	?	?
Mansur 2005	?	?	+	?	-	?	?
Pomeroy 2006	+	+	+	+	+	?	?
Takeuchi 2008	?	?	+	?	+	?	?
Wang 2012	?	+	+	+	+	?	?
Weiduschat 2011	?	+	+	+	+	?	?

Effects of interventions

rTMS versus control

1.1 Activities of daily living

Five trials (Du 2005; Jin 2002; Khedr 2005a; Khedr 2009a; Khedr 2010) with a total of 319 participants recorded activities of daily living but this was recorded at different time points. Data were available for 183 (57.4%, 183/319) participants (Du 2005; Jin 2002). Meta-analysis showed that rTMS treatment was not associated with a significant increase in the Barthel Index score (MD 15.92, 95% CI -2.11 to 33.95). However, there was statistically significant heterogeneity between the trials ($I^2 = 97\%$) (Analysis 1.1).

1.2 Motor function

Eight trials with a total of 173 participants reported motor function of the affected extremities. However, data from four trials were available for 73 participants (42.2%, 73/173) (Fregni 2006; Khedr 2009a; Malcolm 2006; Pomeroy 2006). Meta-analysis showed that rTMS treatment was not associated with a significant improvement in motor function (SMD 0.51, 95% CI -0.99 to 2.01). However, there was statistically significant heterogeneity between trials ($I^2 = 87.6\%$) (Analysis 1.2). In this analysis, we found that one study was visually totally heterogenous to the other studies (Khedr 2009a) and sensitivity analysis removing these data reduced I^2 to 0%, but there was also no significant effect on motor function (SMD -0.29, 95% CI -0.88 to 0.29).

1.3 Death or disability

No data on death or disability at the end of follow-up were available in any of the included trials.

1.4 Any other impairment improvement (e.g. visual, perceptual, depression, cognition, etc)

Two trials with a total of 92 participants reported depression (Chen 2005; Du 2005). Meta-analysis showed that rTMS treatment was not associated with a significant decrease in the Hamilton depression scale score (MD -0.12, 95% CI -13.84 to 13.59). However, there was statistically significant heterogeneity between the trials ($I^2 = 96\%$) (Analysis 1.3).

Two trials with a total of 75 participants reported cognitive function (MMSE score) (Du 2005; Fregni 2006). Meta-analysis

showed that there was no statistically significant difference between the groups (MD 1.87, 95% CI -5.93 to 9.68) (Analysis 1.4).

One trial with 20 participants reported that a two-week course of continuous theta-burst stimulation over the posterior parietal cortex of the left hemisphere may be an effective strategy in accelerating recovery from visuospatial neglect in subacute stroke patients (Koch 2012).

Another trial with 14 participants reported a clinically significant improvement in the rTMS group, with a mean of 19.8 points in the Aachen Aphasia Test total score, whereas the control group did not improve (Weiduschat 2011).

1.5 Adverse outcome

Eight trials (Du 2005; Jin 2002; Khedr 2009a; Khedr 2010; Koch 2012; Takeuchi 2008; Wang 2012; Weiduschat 2011) reported that there were no adverse effects. Six trials reported adverse outcomes: eight transient or mild headaches (2.4%, 8/327) were observed in the rTMS group (Chen 2005; Fregni 2006; Jorge 2004; Khedr 2005a); one participant reported an increase in anxiety (0.3%, 1/327) (Fregni 2006); two participants had single episodes of neurocardiogenic syncope (0.6%, 2/327) with their initial exposure to rTMS (Kirton 2007); an exacerbation of initial insomnia was observed in one participant (0.3%, 1/327) (Jorge 2004); and local discomfort at the site of the stimulation (Jorge 2004; Malcolm 2006). Five trials made no mention of adverse outcomes (Avenanti 2012; Barwood 2011a; Liepert 2007; Mansur 2005; Pomeroy 2006).

2. Subgroup analysis

2.1 Different frequency of stimulation

Subgroup analyses of different stimulation frequencies showed no significant difference between the low-frequency group and the high-frequency group in their effects on motor function (Analysis 2.1).

2.2 Different duration of illness

Subgroup analyses by duration of illness showed no significant difference between 'within 30 days of symptom onset' and 'more than one month' on motor function (Analysis 3.1).

From the available information, it was not possible to perform the originally planned sensitivity analyses because of insufficient numbers of trials.

DISCUSSION

Summary of main results

We included 19 trials involving a total of 588 participants in this review. Two heterogeneous trials (183 participants) assessing the effect of repetitive transcranial magnetic stimulation (rTMS) on activities of daily living showed that rTMS treatment was not associated with a significant increase in the Barthel Index score. Four trials assessing the effect of rTMS on motor function were not found to have a statistically significant effect on motor function. Limited data revealed rTMS may have effects on aphasia and neglect in patients with stroke. Few mild adverse events were observed in the rTMS group, with the most common events being transient or mild headaches and local discomfort at the site of the stimulation.

Overall completeness and applicability of evidence

The results of the review were limited by the following factors.

1. The sample size was small, ranging from 10 to 123 participants, and the small number of participants in each trial may not have adequate power to detect a difference between the two groups. It is necessary to perform large-scale RCTs to verify the efficacy of the intervention. In addition, many of the trials had strict inclusion criteria, which limited the applicability.
2. The stimulation parameters (frequency, intensity, pulses) also varied across studies. The most suitable rTMS protocol is still uncertain.
3. Various motor function assessment measures were used as the primary outcome across the studies, but functional outcome was scarce.
4. Most of the included trials evaluated the outcome at the end of the treatment period or within one month. Whether rTMS had long-term effects on functional recovery was not clear. The short-term follow-up could not detect the long-term effect of rTMS. In consideration of spontaneous recovery after stroke, long-term outcome measurement should be performed (three months or longer) after stroke.
5. Although we included 19 trials in the review, we pooled the three types of controls to a single analysis instead of the three analyses planned in the Methods section, due to limited available data. For example, data from four trials were available for motor function. It was therefore not possible to assess whether there were significant differences in treatment effect in important subgroups such as low frequency compared with high frequency and acute stroke patients compared with chronic patients.
6. There was huge heterogeneity between the studies pooled within the meta-analyses. The potential reasons for this heterogeneity were: (a) the time between stroke and recruitment

varied from four hours to six years; (b) various rTMS protocols were used; and (c) different motor function assessments were used across the studies.

Quality of the evidence

The quality of reporting in general was poor. Most trials only reported 'randomly allocating' participants but the method of randomisation was not described. Only five trials adequately concealed the randomisation sequence. Although 16 trials used sham stimulation in the control group, the success of blinding was not recorded. None of included trials stated that an intention-to-treat analysis had been performed.

Potential biases in the review process

The funnel plots showed a slightly asymmetrical funnel distribution, which indicated likely publication bias. In addition, we cannot deny the possibility that there are additional trials that are unpublished or published in sources not covered by our search.

Agreements and disagreements with other studies or reviews

Recently, a systematic review indicated that rTMS had a positive effect on motor recovery in patients with stroke, and it also found low-frequency rTMS over the unaffected hemisphere may be more beneficial than high-frequency rTMS over the affected hemisphere (Hsu 2012). In contrast, we did not find rTMS to have a statistically significant effect on motor function. However, treatment with rTMS may have effects on aphasia and neglect in patients with stroke. These findings should be clarified in further studies.

AUTHORS' CONCLUSIONS

Implications for practice

Based on this review, the routine use of rTMS for patients with stroke is not recommended until its efficacy is verified in high-quality, large-scale RCTs.

Implications for research

Future studies with larger sample sizes are needed to validate this therapeutic approach. Particularly, the most suitable rTMS protocol should be investigated as a priority. In addition, functional outcome measured at long-term follow-up (at least three months or longer after stroke) should be used as the primary outcome.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Avenanti 2012

Methods	S: computer generated sequence C: unclear B: participants and assessor blinded Ex: none Losses to FU: none
Participants	Country: Italy 30 participants Age: unknown Sex: unknown Chronic stroke patients with mild motor disabilities (> 6 months after the first-ever stroke)
Interventions	Rx: participants received 10 daily sessions of 1 Hz rTMS over the intact motor cortex + before or after PT Control: participants received sham rTMS + before or after PT Duration: 10 days
Outcomes	Jebsen-Taylor Hand Function Test (JHFT), the Nine-Hole Peg Test (NHPT), and the Box and Block test (B&B) were used to assess hand dexterity Maximal force of key grip and tip-pinch was evaluated by means of a pinch-meter Outcomes were assessed for 3 months after the end of treatment Adverse events: unclear
Notes	Ex: moderate to severe motor deficits, any other clinically significant medical comorbidity and epilepsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded.

Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Barwood 2011a

Methods	S: unclear C: unclear B: participants blinded Ex: none Losses to FU: none
Participants	Australia 12 participants Age: rTMS: mean 60.8 ± 5.98 years; control group: 67.0 ± 13.11 years Sex: 75% male Participants had suffered a left middle cerebral artery stroke between 2 and 6 years previously and had residual language impairments
Interventions	Rx: low frequency, 1 Hz rTMS was applied to participants for 20 minutes per day (1200 pulses) Control: sham stimulation Duration: 10 days
Outcomes	Behavioural language outcome measures were taken at baseline and 2 months post-stimulation Adverse events: unclear
Notes	Ex: epilepsy or seizures, metal anywhere in the head, cardiac pacemakers, implanted medication pumps, intracardiac lines, other serious medical conditions including serious heart disease, any medications which lower neural thresholds (tricyclic antidepressants, neuroleptic agents etc). Patients who had suffered multiple strokes were excluded due to increased risk of adverse reactions to stimulation. Those patients who had severe visual or hearing impairments were also excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Barwood 2011a (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Chen 2005

Methods	S: drawing of lots C: unclear B: assessor blinded Ex: none Losses to FU: none
Participants	Country: China 32 participants Age: rTMS: mean 61.3 ± 4.9 years; control group: 61.2 ± 4.7 years Sex: 59.4% male Poststroke depression
Interventions	Rx: 0.5 Hz rTMS was given each side of the prefrontal lobe for 30 stimulations each day + regular treatment Control: regular treatment Duration: 7 days
Outcomes	Hamilton Depression Scale score at 1 week after completing the treatment phase days Adverse events: 1 transient headache was observed in rTMS group
Notes	Ex: intracerebral haemorrhage; aphasic patients with severe language comprehension deficits; seizures; severe systemic disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drawing of lots
Allocation concealment (selection bias)	Unclear risk	Not reported

Chen 2005 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available
Other bias	Unclear risk	None known

Du 2005

Methods	S: drawing of lots C: unclear B: unblinded Ex: none Losses to FU: none	
Participants	Country: China 60 participants Age: mean 57.6 ± 10.8 years (range 56 to 83 years) Sex: 56.7% male Poststroke depression accompanied by cognitive impairment Depression: Hamilton (24 items) ≥ 8; cognitive impairment: MMSE illiteracy ≤ 17, primary school ≤ 20, high school ≤ 24 100% CT or MRI before entry	
Interventions	Rx: low frequency rTMS (0.5Hz) stimulate bilateral frontal lobes with 60% of maximal stimulus intensity, 30 minutes for each side, 1 sequence every day for 5 days as a course Control: baseline treatment alone (vasodilators, neuronutrition and fluoxetine 20mg/d for 8 weeks) Duration: 4 weeks	
Outcomes	Activities of daily life: BI at 8 weeks Hamilton Depression Scale and MMSE at 8 weeks Adverse events: no adverse event was observed	
Notes	Ex: coma, aphasia, history of depression or mental disorders, severe heart disease, pulmonary or renal or hepatic failure	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Du 2005 (Continued)

Random sequence generation (selection bias)	Low risk	Drawing of lots
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Fregni 2006

Methods	S: unclear C: unclear B: participants, investigator and assessor blinded Ex: none Losses to FU: none
Participants	Country: USA 15 participants Age: mean 56 ± 11.5 years Sex: 73.3% male At least 1 year after stroke
Interventions	Rx: participants received 5 sessions of rTMS to the unaffected hemisphere over the primary motor cortex with the following parameters: intensity of 100% MT, frequency of 1 Hz, 1200 stimuli as a single, continuous train lasting 20 minutes Control: a sham coil was placed at the same place and used the same stimulation parameters Duration: 2 weeks
Outcomes	Jebsen-Taylor Hand Function Test (JTT), simple reaction time (sRT), choice reaction time (cRT), and Purdue Pegboard test (PTT) Adverse events: in the active group, 1 participant reported a mild headache (contralateral to the side of TMS application) and 1 participant reported an increase in anxiety. In the sham rTMS group, 1 participant reported an increase in the tiredness and 1 participant reported a mild headache

Fregni 2006 (Continued)

Notes	Ex: any clinically significant or unstable medical disorder, a history of substance abuse, any neuropsychiatric comorbidity other than stroke, and contraindications to rTMS	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigator were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Jin 2002

Methods	S: unclear C: unclear B: unclear Ex: none Losses to FU: none
Participants	Country: China 123 participants Age: rTMS: mean 64.0 ± 7.9 years; control group: 63.5 ± 7.9 years Sex: 47.2% male Acute ischaemic stroke (4 hours to 10 days)
Interventions	Rx: rTMS was given over the affected hemisphere once a day for 14 days + regular treatment Control: regular treatment Duration: 14 days
Outcomes	Fugl-Meyer score and BI were evaluated at the end of treatment Adverse events: all the participants tolerated rTMS well without any adverse effects

Jin 2002 (Continued)

Notes	Ex: epilepsy, brain trauma, severe heart diseases, GCS < 8 and contraindications to rTMS	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Jorge 2004

Methods	S: unclear C: unclear B: participants and assessor blinded Ex: none Losses to FU: none
Participants	Country: USA 20 participants Age: rTMS: mean 63.1 ± 8.1 years; sham rTMS: 66.5 ± 12.2 years Sex: 55% male Poststroke depression who do not respond to antidepressants
Interventions	Rx: receive 10 sessions of active (10 Hz, 110% of the motor threshold, 20 trains of 5 seconds duration) left prefrontal rTMS Control: sham rTMS with the same parameters was applied with the coil angled away from the head to reproduce the noise of the stimulation as well as some local sensation. Duration: 14 days

Jorge 2004 (Continued)

Outcomes	Hamilton Depression Scale score at 1 week after completing the treatment phase days Neuropsychological variables at week 4 Adverse events: transient headaches; local discomfort at the site of the stimulation; an exacerbation of initial insomnia observed in 1 participant
Notes	Ex: severe systemic disease or an ongoing neoplasia, neurodegenerative disorders, patients with clinical evidence of dementia or aphasic patients with severe language comprehension deficits, alcohol or drug abuse during the past 12 months, seizures, major head trauma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Khedr 2005a

Methods	S: unclear C: unclear Participant and assessor blinded Ex: none Losses to FU: none
Participants	Country: Egypt 52 participants Age: rTMS: mean 53.5 ± 9.5 years; sham rTMS: 52.2 ± 8.2 years Sex: 69.2% male Acute ischaemic stroke (middle cerebral artery) 100% CT before entry

Khedr 2005a (Continued)

Interventions	Rx: rTMS consisted of 10 x 10-second trains of 3 Hz stimulation with 50 seconds between each train Control: sham rTMS with the same parameters was applied with the coil angled away from the head to reproduce the noise of the stimulation as well as some local sensation Duration: 10 days
Outcomes	Activities of daily life: BI at 10 days Scandinavian Stroke Scale at 10 days Adverse events: occasional headache
Notes	Ex: unstable cardiac dysrhythmia, and previous administration of tranquilliser, severe aphasia, anosognosia, or cognitive deficit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Khedr 2009a

Methods	S: unclear C: closed envelope B: participants and assessor blinded Ex: none Losses to FU: none
Participants	Country: Egypt 36 participants Age: mean 57.9 ± 11.0 years

	Sex: 52.8% male Acute ischaemic stroke of middle cerebral artery territory (7 to 20 days)
Interventions	Rx: Group 1: participants received real rTMS with 1 Hz continuous, for 15 minutes at 100% of RMT over the unaffected hemisphere with total 900 pulses Group 2: participants received real rTMS with 3 Hz, 10 seconds, 30 trains, inter-train interval 2 seconds with total 900 pulses at 130% of RMT over the affected hemisphere Control: sham rTMS with the same parameters as Group 2 but rTMS was applied with the coil angled away from the head to reproduce the noise of the stimulation as well as some local sensation Duration: 5 days
Outcomes	Hand grip NIHSS BI Pegboard Tasks Score Keyboard Tapping Score All outcomes were evaluated at the end of treatment and 3 months Adverse events: All the participants tolerated rTMS well without any adverse effects
Notes	Ex: extensive infarction, severe flaccid hemiplegia, unstable cardiac dysrhythmia, epilepsy, previous administration of tranquilliser, severe aphasia, anosognosia or cognitive deficit and contraindications to rTMS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Closed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Khedr 2010

Methods	<p>S: unclear</p> <p>C: closed envelope</p> <p>B: participants and assessor blinded</p> <p>Ex: none</p> <p>Losses to FU: 10 participants out of the 48 participants did not complete the follow-up at the end of the year</p>
Participants	<p>Country: Egypt</p> <p>48 participants</p> <p>Age: mean 57.9 ± 11.0 years</p> <p>Sex: 50% male</p> <p>Acute ischaemic stroke of middle cerebral artery territory (5 to 15 days)</p>
Interventions	<p>Rx: Group 1: participants received real rTMS with 3 Hz, 5 seconds, 50 trains, with total 750 pulses at 130% of RMT (of the unaffected hemisphere)</p> <p>Group 2: participants received real rTMS with 10 Hz, 2 seconds, 37 trains, with total 750 pulses at 100% of RMT (of the unaffected hemisphere)</p> <p>Control: participants received sham rTMS with the same parameters of Group 1 but the sessions were applied with the coil angled away from the head to reproduce the noise of the stimulation as well as some local sensation</p> <p>Duration: 5 days</p>
Outcomes	<p>NIHSS</p> <p>mRS</p> <p>All outcomes were evaluated at the end of treatment and 12 months</p> <p>Adverse events: all the participants tolerated rTMS well without any adverse effects</p>
Notes	<p>Ex: extensive infarction, severe flaccid hemiplegia, unstable cardiac dysrhythmia, epilepsy, previous administration of tranquilliser, severe aphasia, anosognosia or cognitive deficit and contraindications to rTMS</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Closed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded

Khedr 2010 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	20.8% participants did not complete the follow-up at the end of the year
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Kirton 2007

Methods	S: hospital identification number C: unclear B: participants and assessor blinded Ex: none Losses to FU: none	
Participants	Country: Canada 10 participants Age: 13.25 years (7-21 years) Sex: 60% male Chronic hemiparesis in subcortical paediatric stroke (mean time post stroke 6.33 ± 3.56 years)	
Interventions	Rx: low frequency rTMS over contralesional motor cortex once per day for 8 days. The TMS coil was held in standard position, parallel to the motor cortex with the handle of the coil pointed backwards at 45° relative to midline Parameters: intensity that was 100% of the rest motor threshold on the non-lesioned side; frequency of 1 Hz; and duration of 20 minutes (1200 stimuli) Control: same as treatment group, but the coil was placed perpendicular to the skull Duration: 8 days	
Outcomes	Melbourne Assessment of Upper Extremity Function Grip strength Purdue Peg Board Test Halstead-Reitan finger tapping Adverse events: no serious adverse events were reported. 2 participants had single episodes of neurocardiogenic syncope with their initial exposure to TMS	
Notes	Ex: neonatal; seizures for more than 1 month post stroke; a movement disorder; current use of drugs that potentially alter cortical excitability; or a disease state with ongoing risk of recurrent stroke (e.g. moyamoya or sickle cell disease)	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participant whose hospital identification number had the lowest final digit (or lowest penultimate digit, if the final digits

Kirton 2007 (Continued)

		of the two participants were the same) was assigned to rTMS treatment, the other to sham
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Koch 2012

Methods	S: unclear C: unclear B: participants, investigator and assessor blinded Ex: 1 in Rx and 1 in control Losses to FU: none
Participants	Italy 20 participants Age: rTMS: mean 61.4 years; control group: 71.9 years Sex: 55.6% male Subacute ischaemic stroke patients (24 - 102 days after the first-ever stroke)
Interventions	Rx: in every session, 3-pulse bursts at 50 Hz repeated every 200 msec for 40 seconds were delivered at 80% of the active motor threshold over the left posterior parietal cortex (PPC) (600 pulses). Every day 2 sessions of left PPC continuous theta-burst stimulation (cTBS) were applied with an interval of 15 minutes Control: sham stimulation was delivered with the coil angled at 90°, with only the edge of the coil resting on the scalp. Stimulus intensity, expressed as a percentage of the maximum stimulator output, was set at 80% active motor threshold for the first dorsal interosseous, inducing the same acoustic sensation as for real TBS Duration: 10 days
Outcomes	Behavioral Inattention Test Scores Outcomes were assessed at the end of treatment and at 1 month follow-up Adverse events: no significant adverse effect was reported

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants did not complete the intervention (1 in the control group and 1 in the experimental group)
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Liepert 2007

Methods	S: unclear C: unclear B: participants and assessor blinded Ex: none Losses to FU: none
Participants	Germany 12 participants Age: mean 63 ± 11 years Sex: 66.7% male Acute subcortical stroke (less than 14 days after the stroke)
Interventions	Rx: inhibitory 1 Hz rTMS over the contralesional M1. Stimulus intensity was subthreshold (90% of motor threshold at rest) Control: sham stimulation. Duration: 20 minutes
Outcomes	Grip strength and Nine-Hole-Peg Test Adverse events: unclear

Liepert 2007 (Continued)

Notes	Ex: dementia, aphasia and all other neurological diseases apart from the stroke, the intake of drugs known to interfere with brain excitability, pregnancy, heart pacemakers and metallic objects in the brain	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Malcolm 2006

Methods	S: unclear C: unclear B: participants and assessor blinded Ex: none Losses to FU: none
Participants	Country: USA 19 participants Age: rTMS: mean 68.4 ± 8.4 years; control group: 65.7 ± 5.1 years Sex: 57.9% male Chronic hemiparesis in subcortical stroke (mean time post stroke 3.8 ± 3.3 years)
Interventions	Rx: participants received 2000 stimulations daily for 10 consecutive weekdays. Each daily treatment of 2000 stimuli was administered as 50 trains of 40 stimuli, stimulus rate of 20 Hz, stimulus train duration of 2 seconds, with an intertrain interval of 28 seconds. Stimulus intensity was 90% of motor threshold + constraint-induced therapy Control: sham rTMS + constraint-induced therapy Duration: 14 days

Malcolm 2006 (Continued)

Outcomes	The primary outcome measures: the Wolf Motor Function Test (WMFT) and the Motor Activity Log (MAL)-Amount of Use Secondary outcome measures including the Box and Block Test (BBT) and the MAL-How Well Adverse events: no discernible adverse effects of rTMS beyond scalp discomfort
Notes	Ex: use of medications that may lower seizure threshold, history of epilepsy, brain tumour, drug or alcohol abuse, dementia, major head trauma or major psychiatric illness, arteriovenous malformation, intracortical haemorrhage, subarachnoid haemorrhage, pregnancy and contraindications to rTMS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Mansur 2005

Methods	S: unclear C: unclear B: participants blinded Ex: 2 participants were excluded Losses to FU: none
Participants	Brazil 10 participants Age: mean 53.3 years Sex: 30% male People within 12 months of a stroke

Interventions	Participants received 3 sessions of rTMS (1 Hz, 100% of motor threshold, 600 pulses) to the unaffected hemisphere over the primary motor (real or sham rTMS) and over the premotor cortex (real rTMS) The order of these different rTMS sessions was randomised and counterbalanced across participants Duration: 10 minutes	
Outcomes	Simple reaction time (sRT) Four-choice reaction time (cRT) Purdue Pegboard Test Finger tapping. Adverse events: unclear	
Notes	Ex: unclear	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants were excluded after randomisation
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Pomeroy 2006

Methods	S: computer generated C: sequentially-numbered opaque envelopes B: participants and assessor blinded Ex: During the treatment stage, 2 participants transferred to another hospital, and 1 withdrew as rTMS produced headache Losses to FU: none
Participants	Country: UK 27 participants Age: mean 74.8 years Sex: 33.3 % male Middle cerebral artery infarct (mean time after stroke was 26.6 days (range 7-85))
Interventions	Rx: real rTMS consisted of 200 1 Hz stimuli at 120% motor threshold in 5 blocks of 40 separated by 3 minutes delivered to the lesioned hemisphere Control: placebo rTMS used a dummy coil Duration: 8 days
Outcomes	Action Research Arm Test (ARAT) Adverse events: not reported
Notes	Ex: contraindications to rTMS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Sequentially-numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	11% participants did not complete the study
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Takeuchi 2008

Methods	S: unclear C: unclear B: participants blinded Ex: none Losses to FU: none
Participants	Country: Japan 20 participants Age: mean 62.3 ± 8.4 years Sex: 80% male Chronic subcortical stroke (more than 6 months duration)
Interventions	Rx: rTMS was applied over the motor cortex of the unaffected hemisphere at a frequency of 1 Hz and a stimulus intensity of 90% rMT measured with Magstim Rapid for 25 minutes (1500 pulses) + motor training Control: sham stimulation was applied over the unaffected hemisphere by positioning the coil perpendicular to the scalp and at the same frequency and intensity used for real rTMS+ motor training Duration: 25 minutes
Outcomes	Pinch force and acceleration Adverse events: no adverse effects were reported
Notes	Ex: severe internal carotid artery stenosis, seizure, and an intracranial metallic implant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions after randomisation or losses to follow-up were reported
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Wang 2012

Methods	S: unclear C: sealed envelopes B: participants and assessor blinded Ex: 2 in Rx and 2 in control Losses to FU: none
Participants	Taiwan 28 participants Age: rTMS: mean 64.90 ± 12.37 years; control group: 62.98 ± 10.88 years Sex: 62.5% male Chronic stroke patients (> 6 months after the first-ever stroke)
Interventions	Rx: rTMS was applied at a 1 Hz frequency over the leg area of the motor cortex of the unaffected hemisphere for 10 minutes + task-oriented training Control: participants received sham rTMS + task-oriented training Duration: 10 days
Outcomes	Lower-extremity Fugl-Meyer score and gait performance Outcomes were assessed at the end of treatment Adverse events: none of the participants reported any adverse events
Notes	Ex: moderate to severe motor deficits, any other clinically significant medical comorbidity and epilepsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants did not complete the intervention (2 in the control group and 2 in the experimental group)
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

Weiduschat 2011

Methods	S: unclear C: sealed envelopes B: participants, investigators and assessor blinded Ex: a participant with amnesic aphasia was also excluded Losses to FU: 3 were lost to follow-up
Participants	Germany 14 participants Age: rTMS: mean 66.6 years; control group: 63.75 years Sex: 50% male Poststroke aphasia in the subacute stage
Interventions	Rx: inhibitory 1 Hz rTMS over the right triangular part of the inferior frontal gyrus + conventional speech and language therapy Control: inhibitory 1 Hz rTMS the vertex + conventional speech and language therapy Duration: 2 weeks
Outcomes	Aachen Aphasia Test Adverse events: no serious adverse effect was reported
Notes	Ex: symptomatic prior cerebrovascular accidents, neurodegenerative or psychiatric disease, epilepsy or electroencephalography-documented epileptic discharges, insulin-dependent diabetes mellitus, renal or liver failure, metal parts in the body, life-threatening diseases, and auditory or visual deficits that might impair testing

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	None known
Other bias	Unclear risk	None known

B: blinding method
 BI: Barthel Index
 C: concealment of allocation
 CT: computerised tomography
 Ex: exclusion
 FU: follow-up
 GCS: Glasgow Coma Scale
 MMSE: Mini-Mental Status Examination
 MRI: magnetic resonance imaging
 mRS: modified Rankin Scale
 NIHSS: National Institutes of Health Stroke Scale
 PT: physical treatment
 RMT: resting motor threshold
 rTMS: repetitive transcranial magnetic stimulation
 Rx: treatment
 S: sequence generation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ackerley 2010	Non-RCT
Acket 2011	Meeting abstract
Barwood 2011	Outcome is outside the scope of the review
Boyd 2010	Meeting abstract
Chang 2010	Pseudo-randomised cross-over trial
Conforto 2010	Meeting abstract
Conforto 2011	Meeting abstract
Cotelli 2011	Confounded (real rTMS for 4 weeks versus placebo rTMS for 2 weeks + real rTMS for 2 weeks)
Davis 2007	Meeting abstract
Fridman 2002	Meeting abstract
Hirayama 2006	Non-RCT
Joel 2008	Meeting abstract
Jorge 2008	Participants without stroke were included in this study

(Continued)

Kakuda 2011	Non-RCT
Kate 2010	Meeting abstract
Khedr 2005	Quasi-RCT
Kim 2006	Pseudo-randomised cross-over trial
Kisten 2004	Meeting abstract
Leflaucheur 2004	Participants without stroke were included in this study
Linsdell 2010	Meeting abstract
Meehan 2011	Pseudo-randomised controlled trial
Nowak 2008	Outcome is outside the scope of the review
Nyffeler 2009	Non-RCT
Ravindran 2003	Intervention is outside the scope of the review
Rektorova 2005	Participants are outside the scope of the review
Routhier 2010	Meeting abstract
Sedlackova 2005	Meeting abstract
Talelli 2007a	Non-RCT
Talelli 2007b	Meeting abstract
Tretriluxana 2009	Meeting abstract
Wang 2010	Meeting abstract
Weiduschat 2009	Meeting abstract
Yoo 2008	Meeting abstract
Yoon 2010	Meeting abstract

RCT: randomised controlled trial

rTMS: repetitive transcranial magnetic stimulation

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00044798

Methods	RCT
Participants	Patients with depression associated with small vascular lesions in the brain (vascular depression) Estimated enrolment: 132
Interventions	Experimental: participants will receive treatment with rTMS and citalopram Active comparator: participants will receive treatment with sham repetitive transcranial magnetic stimulation and citalopram
Outcomes	Primary outcome measures: response rates to treatment; relapse rates; the size, number, and location of the vascular lesions; and the amount of regional brain atrophy (time frame: measured at Week 12)
Notes	ClinicalTrials.gov identifier: NCT00044798

RCT: randomised controlled trial

rTMS: repetitive transcranial magnetic stimulation

Characteristics of ongoing studies *[ordered by study ID]*

Ackerley 2010a

Trial name or title	Sensorimotor integration after theta burst stimulation primed upper-limb training in subcortical stroke patients
Methods	Cross-over RCT
Participants	First-ever subcortical stroke and upper-limb impairment (age > 18 years) Target sample size: 18
Interventions	Theta burst stimulation (TBS) was given intermittently (iTBS) or continuously (cTBS) over the primary motor cortex. iTBS (600 stimuli) is applied for 2 seconds on and 8 seconds off, for a total of 192 seconds. CTBS (600 stimuli) is applied continuously for 40 seconds. Either iTBS, cTBS or sham TBS will be delivered in a randomised order over 3 experimental sessions held at least 1 week apart (wash-out period)
Outcomes	Effect on grip function and arm function
Starting date	1 May 2010
Contact information	Suzanne Ackerley, Department of Sport and Exercise Science, Private Bag 92010, Auckland 1142, New Zealand Tel: +64 9 373 7599 ext 84897; email: s.ackerley@auckland.ac.nz
Notes	http://www.anzctr.org.au/ . 2010 ACTR Number: ACTRN12610000314022

ContraStim 2010

Trial name or title	Repetitive transcranial magnetic stimulation (rTMS) to contralesional hemisphere in patients with stroke for upper limb recovery (ContraStim)
Methods	RCT
Participants	Chronic stroke patients (suffered 3 - 9 months prior to the study) with arm and hand dysfunction (age: 18 - 90 years) Estimated enrolment: 36
Interventions	Experimental: contralesional rTMS with arm rehabilitation. Experimental participants will receive subthreshold or suprathreshold rTMS to contralesional hemisphere for up to 20 minutes at 1 Hz followed by task-oriented arm and hand therapy to affected limb Placebo comparator: sham contralesional rTMS plus arm rehabilitation. Participants will receive sham rTMS to contralesional hemisphere for up to 20 minutes followed by task-oriented arm and hand rehabilitation to affected limb
Outcomes	Primary outcome measures: Action Research Arm Test (time frame: baseline, post-treatment, 1 month, 6 months)
Starting date	January 2010
Contact information	Contact: Michael O Schmitt, email: mschmitt@ric.org Contact: Lynn Rogers, email: lynnrogers2008@u.northwestern.edu The Rehabilitation Institute of Chicago, Chicago, Illinois, United States Principal investigator: Richard L Harvey
Notes	ClinicalTrials.gov Identifier: NCT01049802

Humphreys 2010

Trial name or title	Test of transcranial magnetic stimulation (TMS) intervention on unilateral neglect
Methods	RCT
Participants	Presence of left unilateral neglect after right hemisphere stroke (age: 30 - 90 years) Estimated enrolment: 100
Interventions	Experimental: TMS intervention transcranial magnetic stimulation will be applied at a 1 Hz rate for 20 minutes over the ipsilesional posterior parietal cortex of patients showing left neglect after a right hemisphere stroke Placebo comparator: placebo TMS 1 Hz transcranial magnetic stimulation will be applied over the vertex
Outcomes	Primary outcome measures: standardised measure of visual neglect (time frame: 9 months)
Starting date	October 2010
Contact information	United Kingdom Contact: Glyn Humphreys, email: g.w.humphreys@bham.ac.uk Contact: Adrian Williams, email: adrian.williams@uhb.nhs.uk

Humphreys 2010 (Continued)

Notes	ClinicalTrials.gov Identifier: NCT01174641
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Leker 2008

Trial name or title	Use of deep transcranial magnetic stimulation after stroke (tmstroke)
Methods	RCT
Participants	Acute ischaemic stroke (age:18 - 85 years) Estimated enrolment: 40
Interventions	Deep TMS every alternate day for 14 days (7 treatments) versus sham TMS in acute stroke patients 3 - 5 days from onset
Outcomes	Primary outcome measures: proportion of participants achieving excellent functional outcome as determined by a mRS < 2 and BI > 95 obtained at 3 months after stroke onset (time frame: 2 years)
Starting date	March 2009
Contact information	Contact: Ronen R Leker, email: leker@hadassah.org.il
Notes	ClinicalTrials.gov Identifier: NCT00697645

NINDS 2006

Trial name or title	Influence of Theta Burst Stimulation and carbidopa-levodopa on motor performance in stroke patients
Methods	Experimental, controlled trial
Participants	Ischaemic cerebral infarction more than 6 months prior to testing not involving cortical motor areas (age: 18 - 90 years) Estimated enrolment: 58
Interventions	Transcranial magnetic stimulation (TMS) + carbidopa-levodopa versus TMS + placebo versus sham TMS + carbidopa-levodopa vs sham TMS + placebo
Outcomes	The primary outcome measure will be reaction times (time frame: 8 days)
Starting date	2006
Contact information	Shashi Ravindran, Human Cortical Physiology and Neurorehabilitation Section, NINDS Building 10, Room 5S-208, 10 Center Drive, MSC 1428, Bethesda, MD, USA, email: ravindr@s@ninds.nih.gov
Notes	ISRCTN# NCT00366184

Stinear 2006

Trial name or title	Theta Burst Stimulation to promote balanced brain activity following stroke
Methods	RCT
Participants	First-ever monohemispheric subcortical stroke at least 3 months prior to enrolment, upper limb weakness Target sample size: 20
Interventions	Magnetic brain stimulation applied for up to 2 minutes, once a week, for up to 5 weeks Placebo
Outcomes	Motor cortex excitability, arm and hand function
Starting date	8 September 2006
Contact information	Winston Byblow, Human Motor Control Laboratory Department of Sport and Exercise Science University of Auckland Privity Bag 92019 Auckland, New Zealand, email: w.byblow@auckland.ac.nz
Notes	ACTR Number: ACTRN12605000740695

BI: Barthel Index

mRS: modified Rankin Scale

RCT: randomised controlled trial

rTMS: repetitive Transcranial magnetic stimulation

DATA AND ANALYSES

Comparison 1. rTMS compared with control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Activities of daily living	2	183	Mean Difference (IV, Random, 95% CI)	15.92 [-2.11, 33.95]
1.1 Barthel Index	2	183	Mean Difference (IV, Random, 95% CI)	15.92 [-2.11, 33.95]
2 Motor function	4	73	Std. Mean Difference (IV, Random, 95% CI)	0.51 [-0.99, 2.01]
2.1 Jebsen-Taylor Hand Function Test	1	15	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-1.24, 0.92]
2.2 Pegboard task	1	24	Std. Mean Difference (IV, Random, 95% CI)	2.93 [1.72, 4.14]
2.3 Wolf Motor Function Test	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.80 [-1.74, 0.15]
2.4 Action Research Arm Test	1	15	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.84, 1.23]
3 Depression (Hamilton Depression Scale score)	2	92	Mean Difference (IV, Random, 95% CI)	-0.12 [-13.84, 13.59]
4 Cognitive function (MMSE)	2	75	Mean Difference (IV, Random, 95% CI)	1.87 [-5.93, 9.68]

Comparison 2. Different frequency of stimulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Motor function	4	73	Std. Mean Difference (IV, Random, 95% CI)	0.51 [-0.99, 2.01]
1.1 Low frequency	3	54	Std. Mean Difference (IV, Random, 95% CI)	0.97 [-0.86, 2.79]
1.2 High frequency	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.80 [-1.74, 0.15]

Comparison 3. Different duration of illness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Motor function	4	73	Std. Mean Difference (IV, Random, 95% CI)	0.51 [-0.99, 2.01]
1.1 < 30 days of symptom onset	2	39	Std. Mean Difference (IV, Random, 95% CI)	1.54 [-1.14, 4.23]
1.2 > 30 days of symptom onset	2	34	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.23, 0.19]

Analysis 1.1. Comparison 1 rTMS compared with control, Outcome 1 Activities of daily living.

Review: Repetitive transcranial magnetic stimulation for improving function after stroke

Comparison: 1 rTMS compared with control

Outcome: 1 Activities of daily living

Analysis 1.2. Comparison 1 rTMS compared with control, Outcome 2 Motor function.

Review: Repetitive transcranial magnetic stimulation for improving function after stroke

Comparison: 1 rTMS compared with control

Outcome: 2 Motor function

Analysis 1.3. Comparison 1 rTMS compared with control, Outcome 3 Depression (Hamilton Depression Scale score).

Review: Repetitive transcranial magnetic stimulation for improving function after stroke

Comparison: 1 rTMS compared with control

Outcome: 3 Depression (Hamilton Depression Scale score)

Analysis 1.4. Comparison 1 rTMS compared with control, Outcome 4 Cognitive function (MMSE).

Review: Repetitive transcranial magnetic stimulation for improving function after stroke

Comparison: 1 rTMS compared with control

Outcome: 4 Cognitive function (MMSE)

Analysis 2.1. Comparison 2 Different frequency of stimulation, Outcome 1 Motor function.

Review: Repetitive transcranial magnetic stimulation for improving function after stroke

Comparison: 2 Different frequency of stimulation

Outcome: 1 Motor function

Analysis 3.1. Comparison 3 Different duration of illness, Outcome 1 Motor function.

Review: Repetitive transcranial magnetic stimulation for improving function after stroke

Comparison: 3 Different duration of illness

Outcome: 1 Motor function

APPENDICES

Appendix I. MEDLINE (Ovid) search strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.
3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
7. exp Gait Disorders, Neurologic/
8. or/1-7
9. Transcranial Magnetic Stimulation/
10. Magnetic Field Therapy/
11. Magnetics/
12. Electromagnetic Fields/ or Electromagnetic Phenomena/
13. ((magnet\$ or electromagnet\$ or electro-magnet\$) adj5 (stimulat\$ or field\$ or coil\$)).tw.
14. (TMS or rTMS).tw.
15. or/9-14
16. Randomized Controlled Trials as Topic/
17. random allocation/
18. Controlled Clinical Trials as Topic/
19. control groups/
20. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
21. double-blind method/
22. single-blind method/
23. Placebos/
24. placebo effect/
25. cross-over studies/
26. Therapies, Investigational/
27. Research Design/
28. evaluation studies as topic/
29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
32. (evaluation studies or comparative study).pt.
33. random\$.tw.
34. (controlled adj5 (trial\$ or stud\$)).tw.
35. (clinical\$ adj5 trial\$).tw.
36. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
37. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
38. (therapeutic) adj5 (trial\$ or stud\$)).tw.
39. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
40. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
41. (coin adj5 (flip or flipped or toss\$)).tw.
42. versus.tw.
43. (cross-over or cross over or crossover).tw.
44. placebo\$.tw.
45. sham.tw.

46. (assign\$ or alternate or allocat\$ or counterbalance\$ or multiple baseline).tw.
47. controls.tw.
48. or/16-47
49. 8 and 15 and 48
50. limit 49 to humans

Appendix 2. EMBASE (Ovid) search strategy

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke/
2. stroke unit/ or stroke patient/
3. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.
5. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
6. hemiparesis/ or hemiplegia/ or paresis/
7. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. transcranial magnetic stimulation/
10. magnetic stimulation/ or magnetotherapy/ or magnetism/ or electromagnetic field/ or magnet/ or magnetic field/
11. "magnetic and electromagnetic equipment"/
12. ((magnet\$ or electromagnet\$ or electro-magnet\$) adj5 (stimulat\$ or field\$ or coil\$)).tw.
13. (TMS or rTMS).tw.
14. 9 or 10 or 11 or 12 or 13
15. Randomized Controlled Trial/
16. Randomization/
17. Controlled Study/
18. control group/
19. clinical trial/
20. Crossover Procedure/
21. Double Blind Procedure/
22. Single Blind Procedure/ or triple blind procedure/
23. Parallel Design/
24. placebo/
25. experimental design/ or experimental study/ or quasi experimental study/
26. experimental therapy/
27. research subject/
28. Comparative Study/
29. random\$.tw.
30. (controlled adj5 (trial\$ or stud\$)).tw.
31. (clinical\$ adj5 trial\$).tw.
32. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
33. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
34. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
35. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
36. (coin adj5 (flip or flipped or toss\$)).tw.
37. (cross-over or cross over or crossover).tw.
38. placebo\$.tw.
39. sham.tw.
40. (assign\$ or alternate or allocat\$ or counterbalance\$ or multiple baseline).tw.
41. controls.tw.

42. (treatment\$ adj6 order).tw.
43. or/15-42
44. 8 and 14 and 43
45. limit 44 to human

Appendix 3. CINAHL search strategy

- S19 .S11 and S18
- S18 .S12 or S13 or S16 or S17
- S17 .TI (TMS or rTMS) OR AB (TMS or rTMS)
- S16 .S14 and S15
- S15 .TI (stimulat* or field* or coil*) OR AB (stimulat* or field* or coil*)
- S14 .TI (magnet* or electromagnet* or electro-magnet*) OR AB (magnet* or electromagnet* or electro-magnet*)
- S13 .(MH "Magnetics") OR (MH "Electromagnetics") OR (MH "Electromagnetic Fields")
- S12 .(MH "Magnet Therapy")
- S11 .S1 or S2 or S5 or S8 or S9 or S10
- S10 .TI (hemipleg* or hemipar* or paresis or paretic) or AB (hemipleg* or hemipar* or paresis or paretic)
- S9 .(MH "Hemiplegia")
- S8 .S6 and S7
- S7 .TI (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) or AB (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)
- S6 .TI (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) or AB (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid)
- S5 .S3 and S4
- S4 .TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*)
- S3 .TI (brain* or cerebr* or cerebell* or intracran* or intracerebral) or AB (brain* or cerebr* or cerebell* or intracran* or intracerebral)
- S2 .TI (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH) or AB (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH)
- S1 .(MH "Cerebrovascular Disorders+") or (MH "stroke patients") or (MH "stroke units")

Appendix 4. AMED (Ovid) search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or cerebral infarction/ or cerebral ischemia/ or cerebrovascular accident/ or stroke/
2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.
3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
5. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
6. hemiplegia/
7. 1 or 2 or 3 or 4 or 5 or 6
8. magnetics/ or electromagnetics/ or electromagnetic fields/
9. ((magnet\$ or electromagnet\$ or electro-magnet\$) adj5 (stimulat\$ or field\$ or coil\$)).tw.
10. (TMS or rTMS).tw.
11. 8 or 9 or 10
12. 7 and 11

HISTORY

Protocol first published: Issue 12, 2010

Review first published: Issue 5, 2013

Date	Event	Description
1 February 2011	Amended	Correction to the 'Types of participants' section in the original protocol

CONTRIBUTIONS OF AUTHORS

Drafted the protocol: Zilong Hao, Deren Wang, Yan Zeng, Ming Liu.

Developed a search strategy: Zilong Hao, Deren Wang, Yan Zeng, Ming Liu.

Searched for trials: Zilong Hao, Deren Wang.

Obtained copies of relevant references: Zilong Hao, Deren Wang.

Selected trials for inclusion and appraised the quality of papers: Zilong Hao, Deren Wang, Ming Liu, Yan Zeng.

Extracted data from papers and data management: Zilong Hao, Deren Wang.

Wrote the review and interpreted the results: Zilong Hao, Deren Wang, Yan Zeng, Ming Liu.

The review will be updated by Zilong Hao and Deren Wang.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Centre, Chinese Centre of Evidence-Based Medicine, West China Hospital, Sichuan University, China.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Recovery of Function; *Stroke Rehabilitation; Activities of Daily Living; Motor Activity [physiology]; Randomized Controlled Trials as Topic; Transcranial Magnetic Stimulation [*methods]

MeSH check words

Humans