

# BMJ Open Repetitive transcranial magnetic stimulation for upper limb motor function and activities of daily living in patients with stroke: a protocol of a systematic review and Bayesian network meta-analysis

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## ABSTRACT

**Introduction** Patients with stroke usually suffer from varying degrees of movement dysfunction, which seriously affects their quality of life, especially for the upper limb dysfunction. Therefore, this study aims to compare the effects of different repetitive transcranial magnetic stimulation (rTMS) modalities on upper limb motor function and daily activities in patients with stroke.

**Methods and analysis** Relevant research will be collected systematically from PubMed, Web of Science, Embase, Cochrane Library, ProQuest, Wanfang Database, China National Knowledge Infrastructure and Chinese Scientific and Journal Database (VIP) about randomised controlled trials of rTMS in the stroke treatment range from the establishment to November 2020. Primary outcomes will be obtained from scales measuring the upper limb motor function like Upper Extremity Fugl-Meyer Assessment Scale, Wolf Motor Function Test, Jebsen-Taylor Hand Function Test, Action Research Arm Test and Box and Block Test. The secondary outcomes include modified Barthel Index and adverse events (such as vertigo, headache and epilepsy), with the goal of assessing patients' activities of daily living and the safety of treatment. In order to avoid personal bias in the included studies, two reviewers will conduct the data extraction and quality evaluation independently, and all data analyses will be performed by Generate Mixed Treatment comparison software V.0.14.3 and Stata V.16.0.

**Ethics and dissemination** The network meta-analysis (NMA) in this study does not require ethical approval because the data analysis will be used only to evaluate the rTMS treatment efficacy without patients' private information. In addition, the results will be disseminated in international conference reports and peer-reviewed manuscripts.

**PROSPERO registration number** CRD42020212253.

## INTRODUCTION

As a common disease that seriously threatens human health, stroke is characterised by high incidence, high morbidity, high

## Strengths and limitations of this study

- This is the first comprehensive Bayesian network meta-analysis (NMA) to compare the effects of different repetitive transcranial magnetic stimulation modalities on the upper limb motor function and activities of daily living in stroke patients.
- The NMA contributes to finding out the best stimulation mode and provides preliminary evidence for clinical treatment of stroke patients.
- Bias may exist in the results due to the uneven methodological quality of the literature.
- We will systematically search both Chinese and English databases.

recurrence and high mortality rate, laying heavy economic burdens on patients and their families. It is a major cause of long-term disability in the world.<sup>1</sup> Stroke is often accompanied by abnormal posture control, impaired balance function, abnormal muscle strength and motor dysfunction. Studies show that about 55% and 75% of patients with stroke suffer from upper limb motor dysfunction, limiting their daily activities and negatively affecting their life.<sup>2-4</sup> Thus, this study wants to put forward an effective and safe way to improve limb motor function and activity of daily living in patients with stroke.

Repetitive transcranial magnetic stimulation (rTMS) is a neuroelectrophysiological technique, using a time-varying magnetic field with certain intensity to generate an induced electric field in the brain, depolarising neurons and changing the excitability of the local cortex.<sup>5</sup> According to the frequency, conventional rTMS can be divided into low-frequency stimulation ( $\leq 1$  Hz) and high-frequency stimulation

(>1 Hz).<sup>6,7</sup> Currently, theta-burst stimulation (TBS) has received widespread attention as an emerging patterned rTMS.<sup>8</sup> Based on the difference between stimulation and intermittent time, and the effect on the excitability of the cerebral cortex, TBS can be divided into intermittent TBS (ITBS) with excitatory effects and continuous TBS (CTBS) producing inhibitory effects.<sup>9</sup> The parameters affecting rTMS include stimulation site, frequency, pulse number, etc, among which frequency is the primary factor.<sup>10</sup> Generally, low frequency ( $\leq 1$  Hz) is believed to suppress the excitability of the cerebral motor cortex and cause long-term synaptic inhibition, while high frequency ( $\geq 5$  Hz) can facilitate and excite the cerebral cortex.<sup>11,12</sup> However, this may not apply to all cases, and the specific effect depends on brain activity at the site of stimulation.<sup>13</sup> According to previous studies, the balance of mutual inhibition between the two cerebral hemispheres is broken after stroke, which means that the excitability of affected hemispheres decreases while that of healthy hemispheres increases.<sup>14</sup> Meanwhile, the inhibition of healthy hemispheres on affected hemispheres strengthens, thus affecting the recovery of the upper limb function. Besides, there are also theories suggesting that the activation of the contralateral hemisphere through high-frequency stimulation can promote the reorganisation of brain function and enhance compensatory ability, thereby improving the motor function of patients with stroke.<sup>15,16</sup>

In recent years, there have been related studies observing the effects of the above stimulation on upper limb motor function and activities of daily living in patients with stroke.<sup>17,18</sup> Most evidence were obtained by comparison with routine rehabilitation treatment, while either direct comparisons between different modalities of rTMS are lacking. In addition, some previous traditional meta-analyses have revealed the effectiveness of rTMS on patients with stroke.<sup>19–21</sup> However, limited by the availability of pairwise comparisons between interventions, it is difficult to draw a conclusion about which is the most comparatively effective and safe stimulation modalities. In this case, network meta-analysis (NMA) can provide direct and indirect comparisons among multiple interventions.<sup>22</sup> Therefore, this study attempts to compare the effects of different modalities of rTMS on upper limb motor function and activities of daily living in patients with stroke through NMA with both direct and indirect evidence. The first research question is: what is the most effective rTMS modality on upper limb movement function and activities of daily living in patients with stroke? This is the most important result, which is helpful for clinical selection of the best stimulation modality. The second research question is: how safe are the different modalities of rTMS? Investigating the potential adverse reactions of different stimulation modalities is conducive to the standardised use of rTMS.

## METHODS

The protocol of this systematic review will be developed and reported based on the preferred reporting project of the system review and meta-analysis (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)) guidelines<sup>23</sup> and has been registered in the international system evaluation expected to register (PROSPERO). The research protocol will follow the preferred reporting project guide for system evaluation and meta-analysis.

### Inclusion criteria

#### Types of studies

The publication against the criteria of subjects, interventions, controls and outcome will be evaluated. This study will only involve randomised controlled trials of the effects of rTMS on upper limb motor function and activities of daily living in patients with stroke and focus on studies written in Chinese and English. In addition, incorrect randomised methods, non-randomised controlled trials, case reports and other studies will be excluded.

#### Types of participants

Only patients diagnosed with stroke will be chosen as participants. All subjects must meet the diagnostic criteria of stroke and should be further clinically diagnosed with stroke by CT or MRI. Additionally, they should be over 18 years old with clear consciousness and no cognitive impairment, regardless of their sexes and courses of disease.

#### Types of interventions

Subgroups are included in stimulation groups: the low-frequency rTMS (LF-rTMS) on unaffected side, the high-frequency rTMS (HF-rTMS) on affected side, the HF-rTMS on unaffected side, ITBS and CTBS. The control group will include the routine treatment group and sham stimulation group. The routine treatment group will receive routine rehabilitation treatment, including occupational therapy, physical therapy, exercise therapy, virtual reality technology, orthotics, etc. As for the sham stimulation group, the sound of real stimulation will be simulated during treatment without producing effective magnetic stimulation. Studies on the combination of drugs that relieve spasticity (such as botulinum toxin) will be excluded.

#### Outcome measurements

The primary outcomes will focus on the motor function of the upper limb, while the secondary outcomes will discuss activities of daily living and adverse reactions of patients with stroke.

#### Primary outcomes

The main outcome indicators will be the Upper Extremity Fugl-Meyer Assessment Scale (UE-FMA), Wolf motor function test (WMFT), Jebsen-Taylor Hand Function Test (JTHF), Action Research Arm Test (ARAT), Box and Block Test (BBT) and other scales to measure the

upper limb motor function. UE-FMA consists of 33 items evaluating the motor function of patients' upper limbs, each scored by 0, 1 or 2. A score of 0, 1 and 2 represents complete activity limitation, partial activity limitation and no activity limitation, respectively.<sup>24</sup> Higher scores indicate better upper limb motor function in patients, and the total score is 66. FMA contains upper limb reflex activity, extensor and flexor joint movement, joint movement, dissociation movement, normal reflex activity, stability of the shoulder, elbow and wrist, motor function of fingers, coordination and speed. WMFT is used to evaluate the function of hands in performing task activities with 15 items, including 6 items to evaluate the motor function of upper limbs and 9 items to complete functional tasks.<sup>25</sup> During the test, the time of the patient's action is recorded, and the performance of actions will be scored with a total of 6 grades of 0–5. A higher score corresponds to a better quality of the action completed by the patient. In addition, JTHF mainly evaluates the speed of upper limb movement.<sup>26</sup> It involves seven items: writing, flipping cards, picking up small items into containers, imitating eating, stacking chess pieces, moving large and light objects, and moving large and heavy items. The time to complete each activity will be recorded, and the maximum time allowed for each activity is 180s. BBT measures the number of 1-inch building blocks that subjects move from 1 box to another in a minute, and the larger number reflects better athletic ability.<sup>27</sup> ARAT is designed to evaluate the motor ability of the upper limb after stroke, which consists of four parts: grasp, grip, pinch and gross movement. There are 19 items with each of 4 grades, and the highest aggregate score is 57. Similarly, a higher score indicates better motor ability.<sup>28</sup>

### Secondary outcomes

Secondary outcome indicators will include modified Barthel Index (MBI) and adverse events. MBI is used to measure the activities of daily living of patients, including defecation control, eating, dressing, going upstairs and downstairs, going to the toilet, transferring, walking, bathing and grooming.<sup>29</sup> The full score is 100, and the higher score represents a better ability of daily living. Adverse events include vertigo, epilepsy, headache, sensory abnormalities, etc.

### Exclusion criteria

The following contents were excluded: (1) repeated publication of literature; (2) literature review, cross-over study, cohort study or case–control study; (3) data that cannot be extracted; (4) upper limb motor dysfunction not caused by stroke (eg, trauma, cerebral palsy and Parkinson); (5) inaccessible texts and (6) the rTMS stimulation site except the M1 area.

### Search strategies

We will systematically search the PubMed, Embase, Cochrane Library, Web of Science, ProQuest, China National Knowledge Infrastructure, Wanfang Database

and Chinese Scientific and Journal Database (VIP) for randomised controlled trials of patients with stroke treated by rTMS. The time range will be from inception to November 2020, and the retrieval strategy will be subject words combined with free words. Subject words of stroke, rTMS, TMS will be included in the search. The detail search strategy in PubMed database is as follows: (Stroke (mesh) OR cerebrovascular accident (title/Abstract) OR CVA (Title/Abstract) OR Brain Vascular Accident (Title/Abstract) OR hemiplegia (Title/Abstract) OR (apoplexy (Title/Abstract) OR (hemiparesis (Title/Abstract))) AND (repetitive transcranial magnetic stimulation (Title/Abstract) OR Transcranial Magnetic proposal (title/Abstract) OR TMS (Title/Abstract) OR rTMS (Title/Abstract) OR Theta burst stimulation (Title/Abstract) OR  $\theta$  burst stimulation (Title/Abstract))). The Chinese database will be searched with Chinese counterparts in the same approach.

### Studies selection

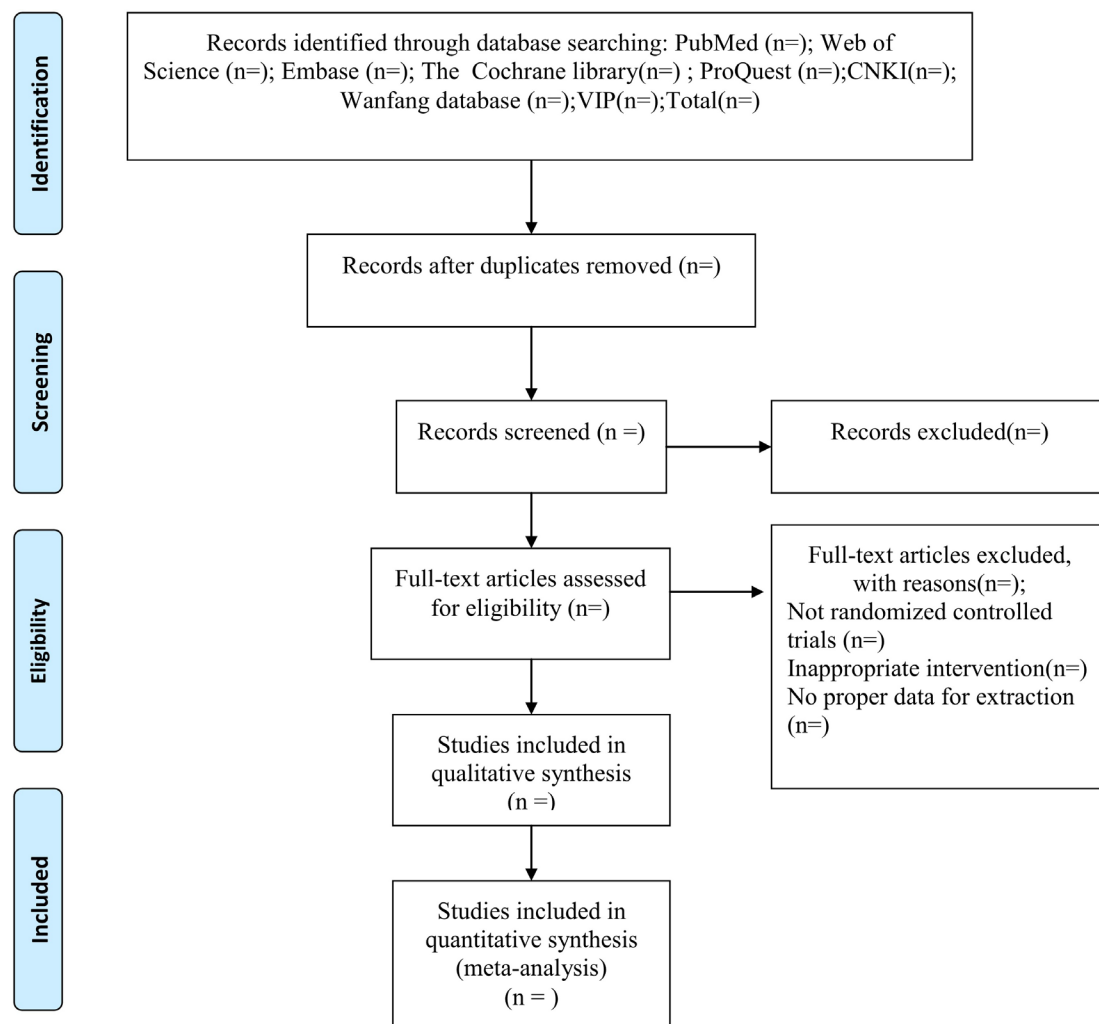
After removing all the repeating documents, two reviewers (YL and YX) will independently select the literature. The two reviewers will select the above inclusion criteria by reading the literature's title and abstract before downloading the full text. Afterward, the two reviewers will pick out literature that satisfies the inclusion criteria by reading the full text. We will contact the author if the selected literature fails to provide complete information or data. Any disagreements in the inclusion process will be handled through a group discussion or consultation with an experienced reviewer (YL). Reasons for the exclusion will be recorded, and the details of the entire literature screening process will be presented in the PRISMA flowchart,<sup>30</sup> as shown in figure 1.

### Data extraction

Two reviewers (XP and ZW) will extract the literature data using previously designed tables from each study. The extracted data contain the first author, year of publication, country of publication, disease course, sample size, age, mode of intervention, duration of intervention, stimulation site and outcome measurements. The inclusion data will be collected by Excel, which the two reviewers will cross-check. As for the missing data, we will contact the author for complete information. In addition, in the case of any disagreement, the research group will discuss and resolve with mutual consensus.

### Risk of bias assessment

Two reviewers (YX and YL) will independently assess the bias risk of the included study using the Cochrane collaborative bias risk tool.<sup>31</sup> The evaluation will include random sequence generation, distribution hiding, blinding subjects and therapists, blinding outcome evaluation, incomplete outcome data, selective reporting results and other biases. The reviewers will assess the bias risk included in the study as low, unclear and high risk under the Cochrane intervention system review manual.



**Figure 1** Flowchart of the study selection process. CNKI, China National Knowledge Infrastructure.

The research group will jointly discuss and resolve any disagreement. Finally, the bias risk diagram will be performed on Revmen V.5.3.

### Grading the quality of evidence

The two reviewers will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the quality of the evidence of the results independently. The GRADE system will include the following five aspects: the limitations, inconsistencies, indirectness, inaccuracies and publication bias of the design.<sup>32</sup> The quality of the evidence will be labelled as ‘high’, ‘medium’, ‘low’ or ‘very low’, according to the rating criteria.<sup>33</sup> An evidentiary overview of the rating results and a table of findings will be generated via GRADE PRO software.

### Dealing with missing data

If the data are missing or unclear, the first author or the corresponding author will be contacted to obtain relevant information. If no reply is received, we will try to calculate the data through the available coefficients. In addition, if the data are reported in the form of a picture, the data will be extracted through Getdata V.2.25. The potential

impact of missing data on the results will be explained in the Discussion section.

### Statistical analysis

Stata V.16.0 will create network diagrams of treatments for patients with stroke and a comparison-adjusted funnel plot for NMA. Dots in the mesh map represent different interventions, and the size of dots represents the sample size; the connection between the dots indicates a direct comparison, and no direct comparison is observed between the two interventions. In addition, the thickness of lines represents the number of studies included. The comparison-adjusted funnel plots will be used to evaluate whether there is a sample effect or publication bias in the included study.

Moreover, we will adopt GeMTC V.0.14.3 software and Markov chain Monte Carlo to carry out Bayesian inference. Considering that the outcome measurements involved in this study are mainly continuous variables, the mean difference and 95% CI will be used as the effect size. The parameters for GeMTC will be set as follows: 3 simulation chains, 10 steps (thinning interval), 50 000 iterations and the first 20 000 are used for annealing to

eliminate the influence of the initial value. The node splitting method is used to test the inconsistency between direct and indirect evidence. When  $p > 0.05$ , the inconsistency is not obvious, enabling the consistency model for data analysis. The convergence between the included studies is expressed by the potential scale reduction parameter (Potential Scale Reduced Factor, PSRF). When the PSRF is close to or equals 1, the convergence should be good. The results with high reliability can be obtained via the consistency model analysis, and the probability ranking plot will help evaluate the curative effect of each intervention method. If the number of included studies is sufficient, subgroup analyses will be performed considering the duration of onset ( $\leq 6$  months and  $> 6$  months), the duration of intervention, the type of stroke (ischaemic and haemorrhagic), the location of onset (basal ganglia, thalamus, brainstem, cerebellum, etc) and the extent of stroke (we will use half of the UE-FMA score as the boundary between mild and severe stroke: UE-FMA score  $< 33$ : severe stroke; UE-FMA score  $\geq 33$ : mild stroke).

### Sensitivity analysis

In order to verify the stability of the results, a sensitivity analysis of the preliminary results will be conducted to evaluate the impact of methodological quality, sample size and missing data on pooled results of this study.

### Publication bias

We will use Egger's test and funnel chart to assess the publication bias of the included major findings. If the funnel diagram is asymmetrical, we will explain the asymmetry of the funnel diagram.

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## DISCUSSION

Patients with stroke are usually inflicted by dysfunction, and that of the upper limb is frequent and seriously affects their quality of life.<sup>34</sup> Thus, the research hotspot in finding an effective and safe way to improve limb motor function and daily activity in patients with stroke. The excitability imbalance of the cerebral hemisphere after stroke is characterised by the abnormal increase of cortical activity on the unaffected side.<sup>35 36</sup> In contrast, the cerebral activity on the affected side will decrease significantly due to the interhemispheric inhibition of the contralateral hemisphere, which seriously impedes the recovery of motor function of the patients.<sup>37 38</sup> rTMS is a non-invasive and relatively safe neuroelectrophysiological technique, which can affect the neuroelectrical activity of the cerebral cortex and regulate the plasticity of the brain. It has been widely used in post-stroke rehabilitation.<sup>39</sup> LF-rTMS on the unaffected side and CTBS can inhibit cortical excitability, while HF-rTMS on the affected side and

ITBS can facilitate and increase cortical excitability.<sup>8 40</sup> Additionally, there are also theories suggesting that the activation of the contralateral hemisphere through high-frequency stimulation can promote the reorganisation of brain function and enhance the compensatory ability of patients with stroke, and this review will include related studies.<sup>15 16</sup> Previous meta-analysis showed that rTMS could improve the upper limb movement and activities of daily living in patients with stroke.<sup>41 42</sup> However, the relevant evidence is obtained by direct comparison (each stimulation group is compared with the control group and the sham stimulation group) instead of systematically comparing different stimulation modalities.

This NMA will include and integrate the latest and most comprehensive literature in this field, aiming to compare the effects of rTMS with different stimulation modalities on the upper limb motor function and activities of daily living in patients with stroke by NMA. Then, this review intends to find out the best stimulation mode accordingly and provide preliminary evidence for the clinical treatment of patients with stroke.

## ETHICS AND DISSEMINATION

The NMA in this study does not require ethical approval because the data analysis will be used only to evaluate the rTMS treatment efficacy without patients' private information. In addition, the results will be disseminated in international conference reports and peer-reviewed manuscripts.

**Contributors** YL, YX and YL conceived the content and drafted the paper. XP and ZW developed the search strategies and conducted data collection. YW provided important suggestions for the revision of the manuscript. YL approved the final version of the manuscript. All authors have approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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