

## Review Article

# The Use of Repetitive Transcranial Magnetic Stimulation for Stroke Rehabilitation: A Systematic Review

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*Objectives:* Stroke is a leading cause of disability. Alternative and more effective techniques for stroke rehabilitation have been sought to overcome limitations of conventional therapies. Repetitive transcranial magnetic stimulation (rTMS) arises as a promising tool in this context. This systematic review aims to provide a state of the art on the application of rTMS in stroke patients and to assess its effectiveness in clinical rehabilitation of motor function. *Methods:* Studies included in this review were identified by searching PubMed and ISI Web of Science. The search terms were (rTMS OR “repetitive transcranial magnetic stimulation”) AND (stroke OR “cerebrovascular accident” OR CVA) AND (rehab OR rehabilitation OR recover\*). The retrieved records were assessed for eligibility and the most relevant features extracted to a summary table. *Results:* Seventy out of 691 records were deemed eligible, according to the selection criteria. The majority of the articles report rTMS showing potential in improving motor function, although some negative reports, all from randomized controlled trials, contradict this claim. Future studies are needed because there is a possibility that a bias for non-publication of negative results may be present. *Conclusions:* rTMS has been shown to be a promising tool for stroke rehabilitation, in spite of the lack of standard operational procedures and harmonization. Efforts should be devoted to provide a greater understanding of the underlying mechanisms and protocol standardization. **Key Words:** Stroke—rehabilitation—repetitive transcranial magnetic stimulation—brain neuromodulation.

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## Introduction

Stroke is a global leading cause of disability<sup>1-10</sup> and the third most frequent cause of death.<sup>11</sup> Between 55% and 75% of patients that had a stroke episode have functional motor limitations that are present even at 3-6 months after its onset,<sup>2,12-14</sup> thereby affecting their quality of life and professional or daily living activities.<sup>4</sup> Physical therapy represents an essential tool for motor recovery; nevertheless, effect sizes of outcomes are frequently limited, in particular when applied to chronic patients.<sup>15</sup> This way, there is a need for more effective approaches for stroke rehabilitation.<sup>16-19</sup>

Under normal conditions, it is believed that a balance of function exists between the hemispheres, regulated by interhemispheric inhibition.<sup>5,6,20</sup> According to the interhemispheric competition model, this balance is affected after stroke; the excitability of the contralesional hemisphere is enhanced, whereas the affected hemisphere undergoes an abnormally increased interhemispheric inhibition.<sup>1,21-24</sup> These excitability changes can be a significant cause for impaired functional recovery.<sup>1,19,25-27</sup> As a result, a possible strategy for stroke rehabilitation is the modulation of plasticity by repetitive transcranial magnetic stimulation (rTMS), seeking to restore the normal activity pattern.<sup>1,19,22</sup>

rTMS is a painless noninvasive brain stimulation tool applied to modulate cortical excitability at the stimulation site and, transsynaptically, at distant sites.<sup>4,5,10,16,22,28-32</sup> Stimulation parameters, mainly frequency,<sup>28,29,31</sup> influence its modulatory effect in terms of resulting excitation or inhibition.<sup>4,11,21,28,33,34</sup> Low-frequency rTMS ( $\leq 1$  Hz) is commonly used to decrease cortical excitability, whereas high-frequency rTMS (often defined as being  $\geq 5$  Hz) is applied to facilitate it.<sup>1,4,10,11,16,20,23,29,32,35-41</sup> Theta burst stimulation (TBS) is a patterned form of rTMS<sup>11,18,21,42</sup> that can also rebalance excitability either by facilitating it (intermittent TBS) or by decreasing it (continuous TBS).<sup>11,42</sup>

This systematic review was conducted to provide a state of the art on the application of different protocols of rTMS in stroke patients and to assess its clinical effectiveness in the rehabilitation of limb motor function following a stroke event.

## Methods

Studies included in this review were identified by searching PubMed and ISI Web of Science. The last search was run on August 9, 2016. The search terms were (rTMS OR "repetitive transcranial magnetic stimulation") AND (stroke OR "cerebrovascular accident" OR CVA) AND (rehab OR rehabilitation OR recover\*). Articles were firstly assessed on the basis of their abstracts and titles. The goal was to include studies that reported applying rTMS to rehabilitate motor impairments on the upper and lower limbs in stroke patients. Simultaneously, exclusion criteria

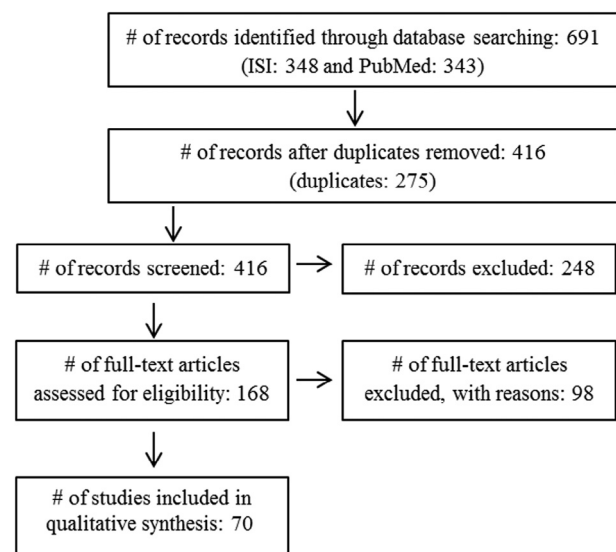
were adopted to reject studies (1) not written in English; (2) performing reviews; (3) in children or adolescents; (4) in animals; (5) recruiting only healthy subjects; (6) with sample size inferior to 5 participants; (7) using paired-pulse or single-pulse TMS instead of rTMS; (8) employing other stimulation techniques instead of TMS; (9) focusing on disease or conditions other than stroke; (10) in which the primary objective was not to evaluate the effect of repetitive TMS on the rehabilitation behavioral outcomes; and (11) not explicitly describing the TMS protocol (including coil, stimulation area, number of sessions, frequency, intensity, and pattern).

A data extraction sheet was developed seeking to retrieve relevant information from each study, notably study design, sample size, participants' clinical characteristics, whether additional therapy was performed, details of the TMS protocol, outcome measures, and behavioral results.

## Results

We identified 691 records through database searching, 275 of which were duplicates (elaborated according to the PRISMA statement requirements<sup>43</sup>; see Figure 1). The remaining 416 articles underwent preliminary screening (of titles and abstracts), with 248 records being excluded because they did not meet the eligibility criteria. After the full-text analysis of each of the 168 individual articles, 70 studies focusing on motor function rehabilitation remained for qualitative synthesis. The studies included for qualitative synthesis were published between 2005 and 2016 and involved a total of 3744 adult patients.

The parameters of rTMS applied to motor recovery in stroke patients and its outcomes are presented in Table 1. Also, we provide clinical sample characterization of patients



**Figure 1.** Search flow (as described in the PRISMA statement). Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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