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Review article

Transcranial magnetic stimulation combined with upper-limb training for improving function after stroke: A systematic review and meta-analysis

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ABSTRACT

Background: Several neuromodulation treatments have been developed, and their effects have been studied in recent years in order to improve neurological rehabilitation after a stroke. The association between upper-limb training and repetitive transcranial magnetic stimulation (rTMS) has provoked controversies and produced inconclusive results.
Objective: The purpose of this study was to investigate the effects of rTMS combined with upper-limb training versus sham rTMS combined with upper-limb training on the upper-limb recovery after a stroke.
Methods: A systematic review with meta-analysis was performed. The eligible studies were randomized controlled trials with stroke subjects, and the outcomes were related to upper-limb motor/functional status and spasticity.
Results: A total of 3234 citations were identified, and 11 studies were included. The meta-analysis included eight studies with 199 participants and did not show any difference between groups, neither for upper-limb function nor for spasticity (upper-limb function [0.03 (95% CI: −0.25 to 0.32; I^2 0%)] and Modified Ashworth Scale [−0.31 (95% CI: −0.78 to 0.17; I^2 43%)]).
Conclusion: The current state of the literature is not enough to support the hypothesis that a combination of rTMS and upper-limb training has a stronger effect on upper-limb function than upper-limb training alone.

Contents

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1. Introduction

Stroke is one of the main causes of long-term neurological disability worldwide [1]. Among those patients who have survived a stroke, it is estimated that around 55–75% will present some degree of long-term sensory-motor impairment [2]. Upper-limb motor ability is commonly affected after a stroke, and in 70% of patients it is responsible for restrictions on functional tasks and daily activities [3,4].

Repetitive transcranial magnetic stimulation (rTMS) is a promising non-invasive neuromodulatory intervention that aims to maximize recovery of function after stroke [5,6]. Two distinct protocols have been employed: excitatory (high-frequency) stimulation of the damaged hemisphere and inhibitory (low-frequency) stimulation of the undamaged hemisphere. rTMS aims to restore the disrupted equilibrium and the inter-hemispheric communication in order to rebalance the inter-hemispheric competition and promote functional recovery [7–9].

In a similar way, motor training is capable of inducing neuroplasticity even in mature brains [10–12]. Rehabilitation approaches induce lasting cortical reorganization in both hemispheres and promote adaptations to the cortical maps [13–16]. Recent studies have shown that upper-limb training procedures such as muscle strengthening, facilitation techniques, task-oriented training, constraint-induced movement therapy and motor imagery may contribute to improving upper-limb motor function in stroke survivors [17,18]. These mechanisms support the reorganization of cortical functions that promote sensory-motor recovery after upper-limb training [7,8,19–23]. Despite the very well-known effect of sensory-motor therapy for stimulating neuroplasticity after stroke, the functional outcome after regular treatments has notable limitations. This is evident since about 50–60% of patients remain with some degree of motor impairment [24].

The association between upper-limb training and rTMS has also been studied [25–36], but the results are still inconclusive. Considering the effects of neuroplasticity, the association between rTMS and upper-limb training may induce more noticeable rehabilitation and upper-limb recovery in post-stroke patients. Therefore, the aim of this systematic review with meta-analysis was to determine the effectiveness of rTMS combined with upper-limb training for promoting upper-limb recovery after a stroke.

Table 1
Literature search strategy used for the PubMed database.

#1 Patient	"Stroke"[Mesh] OR "Stroke" OR "Strokes" OR "Apoplexy" OR "CVA (Cerebrovascular Accident)" OR "CVAs (Cerebrovascular Accident)" OR "Cerebrovascular Accident" OR "Cerebrovascular Accidents" OR "Cerebrovascular Apoplexy" OR "Apoplexy, Cerebrovascular" OR "Cerebrovascular Stroke" OR "Cerebrovascular Strokes" OR "Stroke, Cerebrovascular" OR "Strokes, Cerebrovascular" OR "Vascular Accident, Brain" OR "Brain Vascular Accident" OR "Brain Vascular Accidents" OR "Vascular Accidents, Brain" OR "Cerebral Stroke" OR "Cerebral Strokes" OR "Stroke, Cerebral" OR "Strokes, Cerebral" OR "Stroke, Acute" OR "Acute Stroke" OR "Acute Strokes" OR "Strokes, Acute" OR "Cerebrovascular Accident, Acute" OR "Acute Cerebrovascular Accident" OR "Acute Cerebrovascular Accidents" OR "Cerebrovascular Accidents, Acute"
#2 Intervention 1	"Transcranial magnetic stimulation"[Mesh] OR "Magnetic Stimulation, Transcranial" OR "Magnetic Stimulations, Transcranial" OR "Stimulation, Transcranial Magnetic" OR "Stimulations, Transcranial Magnetic" OR "Transcranial Magnetic Stimulations" OR "Transcranial Magnetic Stimulation, Paired Pulse" OR "Transcranial Magnetic Stimulation, Repetitive" OR "Transcranial Magnetic Stimulation, Single Pulse" OR "rTMS" OR "repetitive transcranial magnetic stimulation" OR "Deep Brain Stimulation" [Mesh] OR "Deep Brain Stimulations" OR "Stimulation, Deep Brain" OR "Stimulations, Deep Brain" OR "Brain Stimulation, Deep" OR "Electrical Stimulation of the Brain" OR "Magnetic Field Therapy" [Mesh] OR "Field Therapies, Magnetic" OR "Field Therapy, Magnetic" OR "Magnetic Field Therapies" OR "Therapies, Magnetic Field" OR "Therapy, Magnetic Field" OR "Magnetic Stimulation Therapy" OR "Magnetic Stimulation Therapies" OR "Stimulation Therapies, Magnetic" OR "Stimulation Therapy, Magnetic" OR "Therapies, Magnetic Stimulation" OR "Therapy, Magnetic Stimulation"
#3 Intervention 2	"Exercise" [Mesh] OR "Exercises" OR "Exercise, Physical" OR "Exercises, Physical" OR "Physical Exercise" OR "Physical Exercises" OR "Exercise, Isometric" OR "Exercises, Isometric" OR "Isometric Exercises" OR "Isometric Exercise" OR "Exercise, Aerobic" OR "Exercise, Aerobic" OR "Aerobic Exercises" OR "Aerobic Exercises" OR "Aerobic Exercise" OR "Physical Therapy Modalities" [Mesh] OR "Modalities, Physical Therapy" OR "Modality, Physical Therapy" OR "Physical Therapy Modality" OR "Physiotherapy (Techniques)" OR "Physiotherapies (Techniques)" OR "Physical Therapy Techniques" OR "Physical Therapy Technique" OR "Techniques, Physical Therapy" OR "Exercise Movement Techniques" [Mesh] OR "Movement Techniques, Exercise" OR "Exercise Movement Technics" OR "Pilates-Based Exercises" OR "Exercises, Pilates-Based" OR "Pilates Based Exercises" OR "Pilates Training" OR "Training, Pilates" OR "Exercise Therapy" [Mesh] OR "Therapy, Exercise" OR "Exercise Therapies" OR "Therapies, Exercise" OR "Occupational Therapy" [Mesh] OR "Therapy, Occupational" OR "Occupational Therapies" OR "Therapies, Occupational" OR "Constraint-induced Movement Therapy" OR "Repetitive Facilitation Exercise" OR "Robot-Assisted training" OR "Mirror Therapy" OR "Task Oriented Training" OR "Strength training" OR "Resistance Training" OR "Physical Rehabilitation" OR "Kinesiotherapy" OR "Range of motion exercise" OR "Bobath" OR "Proprioceptive Neuromuscular Facilitation"
#4 Type of study	#4) Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]
	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos [mh] OR placebo*[tw] OR random*[tw] OR research design [mh: noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR crossover studies [mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal [mh] NOT human [mh])
Search	#1 and #2 and #3 and #4

2. Methods

This systematic review was performed in accordance with the Cochrane Collaboration [37] and is presented according to the suggestions made in the Preferred Reporting Items for Systematic Review and Meta-analyses: The PRISMA Statement [38].

2.1. Search criteria

We conducted an extensive search of the literature up to November 2015 using electronic databases including MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL) and