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REHAB-1085; No. of Pages 11

ARTICLE IN PRESS

Annals of Physical and Rehabilitation Medicine xxx (2017) xxx–xxx

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Review

Changes in transcranial magnetic stimulation outcome measures in response to upper-limb physical training in stroke: A systematic review of randomized controlled trials

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ARTICLE INFO

Article history:
Received 30 January 2017
Accepted 19 April 2017

Keywords:
Transcranial magnetic stimulation
Stroke
Upper-limb physical training
Systematic review
Brain plasticity
Clinical outcome

ABSTRACT

Background: Physical training is known to be an effective intervention to improve sensorimotor impairments after stroke. However, the link between brain plastic changes, assessed by transcranial magnetic stimulation (TMS), and sensorimotor recovery in response to physical training is still misunderstood. We systematically reviewed reports of randomized controlled trials (RCTs) involving the use of TMS over the primary motor cortex (M1) to probe brain plasticity after upper-limb physical training interventions in people with stroke.

Methods: We searched 5 databases for articles published up to October 2016, with additional studies identified by hand-searching. RCTs had to investigate pre/post-intervention changes in at least one TMS outcome measure. Two independent raters assessed the eligibility of potential studies and reviewed the selected articles' quality by using 2 critical appraisal scales.

Results: In total, 14 reports of RCTs (pooled participants = 358; mean 26 $\pm$ 12 per study) met the selection criteria. Overall, 11 studies detected plastic changes with TMS in the presence of clinical improvements after training, and these changes were more often detected in the affected hemisphere by using map area and motor evoked potential (MEP) latency outcome measures. Plastic changes mostly pointed to increased M1/corticospinal excitability and potential interhemispheric rebalancing of M1 excitability, despite sometimes controversial results among studies. Also, the strength of the review observations was affected by heterogeneous TMS methods and upper-limb interventions across studies as well as several sources of bias within the selected studies.

Conclusions: The current evidence encourages the use of TMS outcome measures, especially MEP latency and map area to investigate plastic changes in the brain after upper-limb physical training post-stroke. However, more studies involving rigorous and standardized TMS procedures are needed to validate these observations.

1. Introduction

Annually, millions of people experience a stroke worldwide [1]. In developed countries these days, most people survive a stroke, but many retain chronic sensorimotor impairments that directly affect their functional level and their quality of life as well as that of their relatives [2]. Therefore, improving sensorimotor impairments is a prime target in rehabilitation. The effectiveness of various physical training approaches to foster motor recovery after stroke is now supported by a great number of clinical and randomized controlled trials (RCTs) [3]. Furthermore, evidence from non-invasive neurophysiological measurement tools, such as brain imagery and transcranial magnetic stimulation (TMS), show that improvement in sensorimotor impairments after stroke relies on plastic changes within the central nervous system (CNS), particularly in the sensorimotor cortices of both the ipsi- and contralesional hemispheres [4,5].

TMS represents a particularly relevant tool to assess the CNS because it non-invasively activates superficial cortical cells via a transient time-varying magnetic field [6]. When applied over the primary motor cortex (M1), TMS elicits a motor evoked potential (MEP) in muscles contralateral to the stimulated hemisphere, recorded by electromyography (EMG) [6]. Several measures can be

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http://dx.doi.org/10.1016/j.rehab.2017.04.003

derived from MEP recordings. For example, active or resting motor threshold (AMT or RMT: lowest TMS intensity evoking reliable MEPs in a pre-activated or resting muscle state, respectively) provides information about the membrane excitability of the M1 cortico–cortical axons, whereas the amplitude of the MEP reflects the transsynaptic excitation of corticospinal cells via a complex network of excitatory/inhibitory interneurons [7].

TMS-related measurements are allowing the investigation of corticospinal tract integrity, cortical motor representation of muscles, and intracortical and interhemispheric mechanisms involved in motor control and recovery after stroke [6,8,9]. In people with stroke, the presence of recordable MEPs and their amplitude at baseline can predict motor recovery [10] and response to training [11], respectively. Most importantly, many studies have reported that changes in TMS outcome measures (e.g., change in AMT/RMT or MEP amplitude), from the acute to chronic stages post-stroke, are associated with clinical improvements of sensorimotor impairments throughout recovery, yet results remain conflicting [12].

Furthermore, the literature lacks evidence of the direct investigation of the contribution of physical training to the brain plastic changes probed by TMS. Having a better understanding of the link between clinical and TMS changes in response to training could foster the understanding of CNS adaptations underpinning sensorimotor improvements and in turn might help improve rehabilitation interventions and ultimately, post-stroke functional recovery [5].

Therefore, we performed a systematic review using standardized critical appraisal scales to analyze both the quality and content of RCTs that examined physical training by TMS outcome measures over M1 in people with stroke. The main objective was to determine whether changes in TMS outcome measures paralleled clinical improvements after physical training.

2. Materials and methods

A systematic review (not related to a registered protocol) was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13,14].

2.1. Literature search

We searched the literature in 5 databases (Pubmed, CINAHL, Embase, PEDro, The Cochrane Library) for English or French articles published up to October 2016 by using the following keywords, Pubmed MeSH terms and Embase Emtree in various combinations:

- keywords related to the main theme of "training": training OR 'training"/exp OR exercise OR 'exercise"/exp OR rehabilitation OR 'rehabilitation'/exp OR therapy OR 'therapy'/exp OR physiotherapy OR 'physiotherapy'/exp OR "physical therapy" OR 'physical therapy'/exp OR "occupational therapy" OR 'occupational therapy'/exp;
- keywords related to the main theme of "stroke": stroke OR 'stroke'/exp OR "Stroke" [Mesh];
- keywords related to the main theme of "TMS": "transcranial magnetic stimulation" OR 'transcranial magnetic stimulation'/exp OR "Transcranial Magnetic Stimulation" [Mesh] OR TMS;
- search restrictions using the Boolean operator "NOT": repetitive OR rTMS OR theta OR tDCS OR "transcranial direct current stimulation" OR 'transcranial direct current stimulation'/exp.

The reference lists of selected papers were hand-searched for articles. To ensure the originality of the present review, we searched the 5 databases for other systematic reviews and registered protocols with a similar objective as ours.

2.2. Selection of studies

The lead author (LDB) reviewed the title and abstract of articles retrieved to determine their eligibility according to the following inclusion criteria:

- including people with a stroke;
- testing at least one TMS outcome over M1;
- and with an upper-limb physical training intervention.

The full text of potential articles was then reviewed independently by the 2 authors (L.D.B. and M.H.M.) considering the inclusion criteria and the following exclusion criteria:

- not an RCT;
- no pre/post TMS assessments;
- and physical training not targeting the upper limb and lasting less than 3 days/sessions.

The eligibility of articles was discussed until consensus was reached.

2.3. Critical appraisal of studies

Two standardized critical appraisal tools were used for assessing the quality of the included studies. First, the validated PEDro scale (Physiotherapy Evidence Database from the Centre for Evidence-Based Physiotherapy of The George Institute for Global Health) was used for assessing the quality of the general study design [15]. The scale consists of 11 items that can be rated as "present" or "absent", with a highest possible score of 10. Because the present systematic review specifically focused on TMS outcome measures, only these measures were considered "main outcome measures" when rating the following items: #4 (similar groups at the baseline), #8 (at least 85% retention of participants for one main outcome), #10 (between-group statistical comparisons reported for at least one main outcome) and #11 (both point measures and measures of variability reported for at least one main outcome).

Second, the checklist proposed by Chipchase et al. [16] was used to assess the quality of the TMS methods in included studies. This new appraisal tool was recently used in other systematic reviews and showed good to very good interrater agreement [17,18]. In this scale, the potential sources of methodological bias are probed against 30 factors: 8 related to the participant, 20 to the methodology and 2 to the statistical analysis. Factors are rated as "reported" and/or "controlled" [16]. We adapted the original checklist version to the specific needs of the present review. First, the factor "History of specific repetitive motor activity" was removed because stroke survivors typically undergo several weeks of intensive practice of repetitive movements during rehabilitation. Second, because the review's objective was not to thoroughly characterize all factors affecting the variability of TMS outcome measures (as opposed to [17]), "reported" and "controlled" terms were merged and rated together, by using the following method: for each participant-related factor, a point was allocated for any information given, and for the methodological and analytical factors, a point was given if factors were sufficiently detailed to ensure replication of the methods and if there was no obvious source of methodological bias.

For both critical appraisal tools, the raters independently reviewed the included studies, compared their scores and discussed to reach consensus. Unweighted Cohen's kappa [19,20] was used to evaluate the pre-consensus interrater agreement for each item of both scales and for the total scores of the 2 scales.

Please cite this article in press as: Beaulieu L-D, Milot M-H. Changes in transcranial magnetic stimulation outcome measures in response to upper-limb physical training in stroke: A systematic review of randomized controlled trials. Ann Phys Rehabil Med (2017), http://dx.doi.org/10.1016/j.rehab.2017.04.003