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TMS measures of motor cortex function after stroke: A meta-analysis

Michelle N. McDonnell [a], Cathy M. Stinear [b, *]

[a] School of Health Sciences, Sansom Institute for Health Research, University of South Australia, Adelaide, South Australia, Australia
[b] Department of Medicine, Centre for Brain Research, University of Auckland, Auckland, New Zealand

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) is commonly used to measure the effects of stroke on corticomotor excitability, intracortical function, and interhemispheric interactions. The interhemispheric inhibition model posits that recovery of motor function after stroke is linked to rebalancing of asymmetric interhemispheric inhibition and corticomotor excitability. This model forms the rationale for using neuromodulation techniques to suppress unaffected motor cortex excitability, and facilitate affected motor cortex excitability. However, the evidence base for using neuromodulation techniques to promote post-stroke motor recovery is inconclusive.

Objective: The aim of this meta-analysis was to compare measures of corticomotor excitability, intracortical function, and interhemispheric inhibition, between the affected and unaffected hemispheres of people with stroke, and measures made in healthy adults.

Methods: A literature search was conducted to identify studies that made TMS measures of the motor cortex in adult stroke patients. Two authors independently extracted data, and the quality of included studies was assessed. TMS measures were compared between the affected and unaffected hemispheres of stroke patients, between the affected hemisphere and healthy controls, and between the unaffected hemisphere and healthy controls. Analyses were carried out with data grouped according to the muscle from which responses were recorded, and separately according to time post-stroke (<3 months, and ≥6 months). Meta-analyses were carried out using a random effects model.

Results: There were 844 studies identified, and 112 studies included in the meta-analysis. Results were very similar across muscle groups. Affected hemisphere M1 excitability is lower than unaffected and healthy control M1 excitability after stroke. Affected hemisphere short interval intracortical inhibition (SICI) is lower than unaffected and healthy control SICI early after stroke, and not different in the chronic phase. There were no differences detected between the unaffected hemisphere and healthy controls. There were only seven studies of interhemispheric inhibition that could be included, with no clear effects of hemisphere or time post-stroke.

Conclusions: The neurophysiological effects of stroke are primarily localised to the affected hemisphere, and there is no clear evidence for hyper-excitability of the unaffected hemisphere or imbalanced interhemispheric inhibition. This indicates that facilitating affected M1 excitability directly may be more beneficial than suppressing unaffected M1 excitability for promoting post-stroke recovery.

Introduction

Transcranial magnetic stimulation (TMS) is a commonly used tool for understanding how stroke affects the motor system, and how this system recovers after stroke. TMS has been used to measure primary motor cortex (M1) excitability and intracortical function in both the affected (AH) and unaffected (UH) hemispheres of people with stroke, and these are often compared with the same measures made in healthy age-matched adults. These measures include resting and active motor threshold (RMT, AMT), motor evoked potential (MEP) amplitude and latency, central motor conduction time (CMCT), M1 map volume, short interval intracortical inhibition (SICI) and intracortical facilitation (ICF), and cortical silent period (CSP) [1]. Interhemispheric inhibition has also been evaluated, with dual-coil paired-pulse paradigms as well as ipsilateral silent periods. The affected M1 is typically less excitable

* Corresponding author. Department of Medicine, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.
E-mail address: c.stinear@auckland.ac.nz (C.M. Stinear).

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than the unaffected motor cortex, and better motor performance is associated with more normal and symmetric M1 excitability between the hemispheres [1].

A seminal study noted two patterns of neurophysiological reorganisation between two and four months after stroke [2]. Over this time period, patients in whom AH M1 excitability increased ($n = 13$) also exhibited a decrease in UH M1 excitability, while patients with absent MEPs in the paretic hand ($n = 4$) exhibited an increase in UH M1 excitability. This study may have under-sampled by contemporary standards, as only four MEPs were recorded at each time point [2]. Nevertheless, an increase in AH M1 excitability and a decrease in UH M1 excitability were established as important factors in the recovery of motor function after stroke. Subsequent studies built upon the 'balancing' concept, and explored interhemispheric inhibition (IHI) as a possible mechanism [e.g. Refs. [3–5]].

The interhemispheric imbalance model forms the basis for using neuromodulation techniques, such as repetitive TMS and transcranial direct current stimulation (tDCS), as treatment tools in stroke rehabilitation [6,7]. These techniques are typically used to facilitate the excitability of the AH M1 directly with high-frequency rTMS, or anodal tDCS, and suppress the excitability of the UH M1 with low-frequency rTMS or cathodal tDCS [6,7]. The latter may also reduce the interhemispheric inhibition passed from the UH to AH, and indirectly facilitate AH M1 excitability.

A recent review identified 141 rTMS and 132 tDCS studies for limb impairment after stroke, and concluded that the evidence does not yet support the use of these techniques in routine rehabilitation practice [6]. The mixed results produced by neuromodulation studies to date may be related to small sample sizes, the wide range of stimulation parameters used, and heterogeneity in the time post-stroke at which patients were tested. It may also be the case that suppressing UH M1 excitability is not appropriate for a heterogeneous sample of stroke survivors. Many studies are based on the assumption that hyperexcitability of the UH M1, and its excessive inhibition of the AH M1 via transcallosal connections, causally contribute to ongoing impairment of the paretic limb. This may not be the case for all patients, particularly those with more severe impairment, who may be relying on uncrossed projections from the UH to support proximal control of the paretic limbs. There is some evidence that suppressing UH M1 excitability in these patients is deleterious [8], which has prompted alternative models of neurophysiological reorganisation after stroke that account for the severity of damage to the corticomotor system [7].

A further consideration is the time of testing relative to stroke symptom onset. Corticomotor excitability, intracortical function, and interhemispheric inhibition can be expected to change over time as a result of the neurobiological mechanisms of recovery, and in response to altered patterns of limb use after stroke. The aim of this meta-analysis was to evaluate the interhemispheric imbalance model by comparing measures of corticomotor excitability, intracortical function, and interhemispheric inhibition, between the AH and UH of people with stroke, and measures made in healthy adults. The evolution of these measures over time was considered by comparing data obtained within the first 90 days post-stroke with data obtained 6 months or more post-stroke.

Methods

Types of studies

Studies were included if they used TMS to investigate M1 physiology at rest in people with stroke, with or without a healthy control group. Studies reported TMS parameters in the AH and UH within patients, or in either hemisphere of patients and healthy adults. In the event that the study involved longitudinal measures, or an intervention was applied, only the baseline measures were included for analysis.

Types of participants

Adults (aged $\geq$ 18 years, dependent on database search terms) with a confirmed diagnosis of stroke of any type, and at any time point post-stroke. Healthy adults were also included in the analyses if the study included stroke patients and a control non-stroke group.

Types of measures

Any documented TMS measures were considered for meta-analysis, such as RMT, MEP amplitude and latency, SICI, and ICF, if they were obtained from distal upper limb muscles (hand or forearm). Operational definitions for TMS outcomes, and the common methods employed to collect data, are detailed in Appendix A.

Search strategy

The search strategy was formulated in consultation with a medical librarian, and the Medline strategy used is documented in Table 1. This strategy was adapted as required for each database. We searched the following databases from inception until April 2016: Medline, Cochrane Stroke Group Trials Register, EMBASE, CINAHL, Pedro.

Exclusion criteria

Studies were excluded if the stroke affected the cerebellum exclusively, and if the TMS measures were recorded from the proximal arm muscles (such as biceps brachii), from active muscles, or from the lower limb/pharyngeal/trunk muscles. In the event that studies reported TMS measures from multiple muscle groups, only the distal arm muscle data were included. Case studies were also excluded.

Selection of studies

Two researchers ran each database search independently and then compared findings. Search results were imported into Endnote and duplicates removed. The same two researchers screened the search findings for eligibility, using article titles and abstracts, for inclusion of appropriate participants, measures and use of comparators. When it was unclear if the study met all of the inclusion criteria on the initial title/abstract screening, the full text was obtained and assessed for eligibility.

Data extraction and management

Two authors independently extracted data from the included studies using a standardized data extraction form specifically designed and piloted for this review. Extracted data included the following information: aim of the study, detailed description of the participants, their age, sex, type of stroke and time since stroke, functional abilities, research methods and data collection.

Critical appraisal and sensitivity analysis

We assessed the quality of the included articles based on a proposed methodological checklist [9]. Three items were removed, as they were either irrelevant to this study (time between days of testing) or not reported by any of the studies (prior motor activity of