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Review

Transcranial magnetic stimulation (TMS) in stroke: Ready for clinical practice?

Marie-Claire Smith, Cathy M. Stinear *

Department of Medicine, University of Auckland, Private Bag 92019, AK 1142, New Zealand
Centre for Brain Research, University of Auckland, AK 1142, New Zealand

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ABSTRACT

The use of transcranial magnetic stimulation (TMS) in stroke research has increased dramatically over the last decade with two emerging and potentially useful functions identified. Firstly, the use of single pulse TMS as a tool for predicting recovery of motor function after stroke, and secondly, the use of repetitive TMS (rTMS) as a treatment adjunct aimed at modifying the excitability of the motor cortex in preparation for rehabilitation. This review discusses recent advances in the use of TMS in both prediction and treatment after stroke. Prediction of recovery after stroke is a complex process and the use of TMS alone is not sufficient to provide accurate prediction for an individual after stroke. However, when applied in conjunction with other tools such as clinical assessment and MRI, accuracy of prediction using TMS is increased. rTMS temporarily modulates cortical excitability after stroke. Very few rTMS studies are completed in the acute or sub-acute stages after stroke and the translation of altered cortical excitability into gains in motor function are modest, with little evidence of long term effects. Although gains have been made in both of these areas, further investigation is needed before these techniques can be applied in routine clinical care.

1. Introduction

Stroke is a leading cause of disability with up to 50% of stroke survivors experiencing ongoing disability, and up to 30% still requiring assistance with activities of daily living 6 months after stroke [1]. Although significant progress has been made in the diagnosis, prevention and treatment of stroke, more research into targeted rehabilitation is recommended [2]. One of the emerging techniques which may assist in targeting rehabilitation after stroke is transcranial magnetic stimulation (TMS).

TMS is a non-invasive and painless technique which, when applied over the primary motor cortex (M1), generates a descending volley in the corticospinal pathway, and elicits a motor evoked potential (MEP) in muscles of the contralateral limb [3]. The presence or absence of MEPs early after stroke provides information about the functional integrity of the corticospinal tract (CST) [4,5]. The amplitude and latency of the MEP are measures of the excitability of the corticomotor system.

The use of TMS in stroke research has increased dramatically in the last 20 years, although studies are primarily limited to chronic stroke patients (> 6 months post-stroke) and recording MEPs from the upper limb (UL). Few studies have used TMS to record MEPs from the lower limb (LL) after stroke. The purpose of this review is to describe recent advances in the use of TMS in predicting both the resolution of impairment and the recovery of motor function after stroke. The second part of this review will describe the use of TMS as a treatment modality for rehabilitation of the motor system.

2. Prognosis

Recovery of motor function after stroke is a complex process [6] which is difficult to predict from clinical assessment alone [7]. Despite this, clinical assessment continues to be an important tool in providing an indication of prognosis. There is a strong relationship between the degree of early motor impairment and recovery of function in groups of patients [8–11]. However, there is also large inter-individual variability, which makes prediction of recovery for each individual difficult [10,12–15]. Nijland et al. [7] asked experienced physiotherapists to predict the recovery of arm function in 131 stroke patients. Therapists predicted functional outcome based on the Action Research Arm Test (ARAT): 1) no recovery of hand function, (ARAT < 10/57); 2) recovery of some arm and hand function but not a full recovery

* Corresponding author. Tel.: +64 9 923 3779; fax: +64 9 367 7146.
E-mail address: c.stinear@auckland.ac.nz (C.M. Stinear).

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(ARAT 10 – 56/57); or 3) full recovery of arm and hand function (ARAT = 57). Predictions made ⩽ 72 hrs after stroke were only 60% accurate, with 20% too optimistic, and 20% too pessimistic. The number of years of clinical experience did not affect the accuracy of physiotherapists' predictions [7]. This wide variation in recovery from similar baseline clinical presentations highlights the challenge that clinicians face in predicting recovery of motor function. TMS may provide additional information to explain individual variability and enable a more accurate prognosis.

TMS is used to test the functional integrity and excitability of the corticomotor pathway from the ipsilesional M1 to the affected limb [5]. The ability to elicit a MEP in the paretic UL indicates a functional corticospinal tract (CST), and is associated with greater potential for recovery [13,16–18]. The use of TMS in the early prediction of motor recovery after stroke is a relatively new procedure and many questions remain regarding who this technique is suitable for, how soon after stroke is optimal for testing, whether it can be used equally effectively in both the LL and UL, and which other assessment tools can be used in conjunction with it to provide the most accurate prognosis.

A systematic review by Bembenek et al. [19], found only 15 studies investigating the use of TMS within 2 weeks after stroke as a predictive tool for UL motor recovery, revealing a paucity of research in this area. However, 14 of these studies supported the use of TMS as a predictive tool within this time frame. Research in the LL is even more limited. We found only three studies investigating TMS as a predictor of walking conducted within one month of stroke [20–22]. This lack of research may be due to several factors such as difficulty accessing the LL motor cortex resulting in higher stimulus intensities required than the UL [23], and because the importance of CST integrity in the recovery of ambulation after stroke remains unclear [24]. Due to the lack of literature, it is not possible to draw any conclusions at this stage on the use of TMS as a predictive tool for walking. Therefore, this section of the review will focus on prediction of recovery of UL motor function.

Motor recovery after stroke can be considered in two ways: resolution of impairment (recovery of strength and movement) and recovery of function (the ability to use the hand and arm in daily activities). This is an important distinction to make when reviewing the literature, as there may be different mechanisms contributing to each aspect of recovery [25,26] and results may differ depending on whether the outcome measure assesses impairment or function.

The "proportional recovery rule" can be used to predict resolution of impairment. Prabhakaran et al. [25] measured the resolution of impairment by assessing 41 stroke patients at baseline (24 – 72 h) and again 3 and 6 months after stroke with the Fugl–Meyer UL scale (FM). The individual's "maximal potential recovery" (MPR) was defined as the difference between the maximum FM score possible and baseline score at 24 – 72 h. For example, if a patient scores 26/66 on their baseline FM, their MPR is 66 − 26 = 40. Through linear regression modelling, the authors discovered that baseline FM was the only significant predictor of change in FM at 6 months, and that most participants achieved approximately 70% of their MPR, regardless of baseline FM score [25]. In our example, this means that although the MPR is 40, the change in FM is predicted to be 0.7 × 40 = 28, for a final FM score of 26 + 28 = 54. Prabhakaran et al. [25] postulated that this almost fixed level of improvement must be due to a spontaneous biological process of neurological recovery rather than external influences.

Prabhakaran et al. [25] found that a small group of participants with the lowest baseline FM score did not achieve proportional recovery. Several other studies have since replicated this work, with similar results [27–30]. Why do some participants fail to follow this rule and can we more effectively identify these participants?

Byblow et al. [26] were the first to use TMS to differentiate between those who did, and those who did not, experience proportional resolution of impairment. They demonstrated that the proportional recovery rule only applies to patients who had MEPs in their UL, regardless of baseline FM score. This confirms that the ipsilesional CST must be viable for the proportional rule to apply, and indicates that TMS may be useful soon after stroke to predict resolution of impairment.

Interestingly, UL therapy dose did not influence proportional resolution of motor impairment in patients with MEPs in this study [26]. This finding supports the theory that this aspect of recovery is fundamentally biological. This is a potentially challenging concept for clinicians and warrants further investigation. It is worth noting that proportional recovery only reflects resolution of *impairment*. It does not reflect recovery of *function*. Therapy plays an essential role in recognising the improvements in impairment as they spontaneously occur, and teaching the patient to use the UL in functional activities from the earliest possible stage.

Predicting recovery of function is important in stroke as it is *functional* recovery, rather than impairment, which dictates whether a stroke patient is able to participate in their normal activities. Early studies [16–18] made the observation that overall, patients with MEPs experienced a better recovery in UL function than those without MEPs. However, TMS alone is not sufficient to provide an accurate prognosis for every patient.

Stinear [12] suggested that although clinical assessment, TMS, and MRI each have merits in the prediction of recovery early after stroke, none of them in isolation provide a sufficiently accurate individual prognosis. They proposed an algorithm for predicting the recovery of UL function using a combination of all three (PREP algorithm). This novel sequential approach means that not all patients require all assessments, and begins with the simplest and cheapest bedside assessment which can be completed by all clinicians.

Previous work by Nijland et al. [9] found that clinical assessment of finger extension and shoulder abduction within 72 hours of stroke was a strong predictor for the return of some dexterity. However, they quantified "some dexterity" of the UL as an ARAT score of ⩾ 10. An ARAT score ⩾ 10 indicates that participants gained at least a flicker of hand movement by 6 months, and it was unclear how many were actually able to use the UL functionally in everyday activities. Stinear [12] built on this work and created a specific score called the SAFE score (SAFE = shoulder abduction, finger extension). This score is used in the PREP algorithm to make predictions for individual patients. Those who scored a sum of eight or more out of ten on the medical research council (MRC) scale for shoulder abduction and finger extension within 72 hours of stroke onset were predicted to have a complete recovery of UL function at 12 weeks [13]. TMS was used for patients with SAFE ⩽ 7 to determine if they had MEPs. If MEPs were present, they were predicted to have a notable recovery of UL function by 12 weeks. If MEPs were absent, MRI was used to determine which patients had limited potential for recovery and which had none [12,13].

Using the PREP algorithm, Stinear et al. [13] reported that 60% of patients needed TMS and only 20% required MRI. This reflects a significant saving in expenditure compared with the use of MRI alone. TMS was not required for 40% of patients who could be given a prognosis with the SAFE score. As this was the first study of its kind, the algorithm requires further testing and refining before being used in a clinical setting. Questions remain, such as whether the motor impairment threshold for TMS testing (⩽ 7 on MRC) is at the optimal level, whether therapy dose has an impact on reaching the predicted potential and whether these results in a relatively small sample of 40 participants can be extrapolated to the general stroke population. The authors acknowledge that there was only a