**Transcranial Magnetic Stimulation (TMS) in stroke: ready for clinical practice?**

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**Conflicts of Interest**

The authors declare no conflicts of interest.

**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 magnetic resonance imaging (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.

**Keywords**

Stroke; Transcranial magnetic stimulation; Prognosis; Rehabilitation; Motor

**Introduction**

Stroke is a leading cause of disability [1] with up to 50% of stroke survivors experiencing ongoing disability, and up to 30% still requiring assistance with activities of daily living six months after stroke [2]. Although significant progress has been made in the diagnosis, prevention and treatment of stroke, more research into targeted rehabilitation is recommended [3]. 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 can be used to deliver a focal electromagnetic pulse to the primary motor cortex (M1). This generates a descending volley in the corticospinal pathway, and elicits a motor evoked potential (MEP) in the target muscles of the contralateral limb [4]. The presence or absence of MEPs early after stroke provides information about the functional integrity of the corticospinal tract (CST), which may help in prognosis after stroke [5-7]. The amplitude and latency of the MEP is used as a measure of the excitability of the corticomotor system. This is an established method for testing the effect of new protocols aimed at altering the excitability of the cortex [6, 8].

The use of TMS in stroke research has increased dramatically in the last 20 years. A search of the PubMed database reveals that in 1990, only one study was published on TMS in stroke, whereas in 2010, 99 studies were published. This indicates an increased interest in TMS, although the scope of the research is primarily limited to chronic stroke patients (> 6 months post-stroke) and recording MEPs from the upper limb (UL). There are few studies that 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.

**Prognosis**

Recovery of motor function after stroke is a complex process [9] which is difficult to predict from clinical assessment alone [10]. Despite this, many clinical decisions are based on this prognosis and bedside assessment is often the only assessment tool available in a clinical setting. The ability to accurately predict an individual's functional recovery is vital in assisting clinicians and patients to set realistic rehabilitation goals and in planning the rehabilitation programme and discharge destination [11-13].

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 [14-18]. However, there is also large inter-individual variability, which makes prediction of recovery for each individual difficult [7, 12, 18-20]. In a study by Nijland et al. [10], 20 experienced physiotherapists were asked to predict the recovery of arm function in 131 stroke patients. The Action Research Arm Test (ARAT), which has a maximum score of 57, was used to measure hand and arm function at six months after stroke. Therapists predicted functional outcome for each patient by putting them into one of three categories: 1) no recovery of hand function, but possibly some proximal arm function (ARAT < 10); 2) recovery of some arm and hand function but not a full recovery (ARAT 10-56); or 3) full recovery of arm and hand function (ARAT = 57). Predictions made by the physiotherapists ≤ 72 hrs after stroke were only 60% accurate, with 20% too optimistic, and 20% too pessimistic. Of particular note, the prediction for the second group (patients recovering some hand function but not a complete recovery) was

only 47% accurate despite this group having by far the widest range on the ARAT scale (10-56 out of a maximum of 57 points). Another interesting finding from this study is that the number of years of experience each physiotherapist had in stroke rehabilitation did not affect the accuracy of their predictions for arm recovery [10].

Stinear et al. [7] demonstrated large inter-individual variability in recovery by using the ARAT to measure UL function in patients two weeks after stroke. They found that, of the participants who scored zero (no movement at the hand or arm) on the ARAT at two weeks, some went on to make a notable recovery of UL function by 12 weeks, while others made no recovery at all. This huge variation in recovery from the same baseline clinical presentation highlights the challenge that clinicians face in predicting recovery of motor function after stroke. TMS may provide additional information to explain and predict the individual variability in these groups of patients, enabling 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 [6]. The ability to elicit a MEP in the target muscle in the UL indicates that the descending white matter pathways have been spared, and is associated with greater potential for recovery [7, 21-23]. The use of TMS in the early prediction of motor recovery after stroke is a relatively new procedure and many questions remain about 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. [24], found only 15 studies investigating the use of TMS as a predictive tool for motor recovery of the UL within two weeks of stroke onset, revealing a paucity of research in this area. However, 14 of these 15 studies did

provide evidence to support the use of TMS as a predictive tool for UL motor recovery within this time frame. Research in the lower limb (LL) is even more limited than the UL. We found only two studies investigating TMS as a predictor of walking conducted within one month of stroke onset [25, 26], and one study conducted within one week of stroke onset [27]. This lack of research into the use of TMS as a predictor in the LL may be due to several factors such as difficulty accessing the LL motor cortex, resulting in higher stimulus intensities required than the UL [28], and because the importance of CST integrity in the recovery of ambulation after stroke remains unclear [29]. Due to the lack of literature on TMS in the LL, it is not possible to draw any conclusions at this stage on the use of TMS as a predictive tool in the LL. Therefore, this section of the review will refer to prediction of recovery of motor function in the UL only.

Motor recovery after stroke can be separated into two categories: Resolution of impairment (the ability to move the hand or arm, or recovery of strength) 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 [30-32] and results may differ depending on whether the outcome measure is assessing impairment or function. TMS has a role in predicting both the resolution of motor impairment after stroke and in predicting the return of functional use of the arm.

A recent discovery in predicting resolution of impairment is the Proportional Recovery Rule. Prabhakaran et al. [30] measured the resolution of impairment by assessing 41 stroke patients at baseline (24 – 72 h) and again three and six months after stroke with the Fugl-Meyer UL assessment score (FM). The FM is a highly reliable impairment-based

measure with a maximum score of 66 for the UL [33]. Prabhakaran et al. [30] defined the individual's "Maximal Potential Recovery" as the difference between the maximum FM score possible (66 points) and baseline score at 24-72 hrs: Maximal Potential Recovery (MPR) = 66 – baseline FM. For example, if a patient scores 26/66 on their baseline FM, their MPR (and therefore their maximum possible ΔFM) is 66 - 26 = 40. The authors conducted linear regression modelling of *actual* ΔFM using clinical predictors and magnetic resonance imaging (MRI) of infarct location and size, to analyse which factors influenced each individual's *actual* ΔFM score. They discovered that not only was baseline FM the only significant predictor of ΔFM, but that most participants, regardless of baseline FM score, achieved approximately 70% of their MPR. In our earlier example, this would mean that although the MPR was 40, the *actual* ΔFM was 0.7 x 40 = 28. This phenomenon has been called the Proportional Recovery Rule. Prabhakaran et al. [30] postulated that this almost fixed level of improvement must be due to a spontaneous biological process of motor recovery rather than external influences.

Prabhakaran et al. [30] found that a small group of participants did not achieve proportional recovery, and these were the participants with the lowest baseline FM score (greatest initial impairment). Several other authors have since replicated this work, with similar results [34-37]. Each of these authors proposed a different minimal required FM score for participants to achieve proportional recovery, excluding the more severely impaired patients from analysis. However, as previously discussed, clinical assessment alone has limitations as a prognostic tool [7, 38]. This raises the questions: firstly, what are the mechanisms of this proportional recovery process, and secondly, why do some participants fail to follow this rule and can we more effectively identify who they are?

Byblow et al. [31] suggest that the biological mechanism behind proportional recovery may be related to re-myelination of axons in the CST after stroke. Ischaemic damage from the stroke causes demyelination of some of the surviving axons [39] and motor impairment may improve as the axons undergo re-myelination. Byblow et al. [31] noted that the timeframe of 12 weeks for spontaneous proportional recovery was the same as re-myelination of the damaged axons. Byblow et al. [31] were also the first to use TMS to differentiate between those who did, and those who did not experience proportional recovery of impairment. They demonstrated that the proportional recovery rule only applies to patients who had MEPs in their UL, confirming that the ipsilesional CST must be viable for the proportional rule to apply. They were also able to demonstrate that proportional recovery occurred regardless of baseline FM score (provided the patient had MEPs). This provides early evidence that TMS may be useful soon after stroke to predict resolution of impairment (as measured by ΔFM score).

Interestingly, UL therapy dose did not influence proportional resolution of motor impairment in patients with MEPs in this study, despite a wide range from 0 – 803 minutes [31]. This finding supports the theory that this aspect of recovery is fundamentally biological, and not improved by current clinical practice. This is a potentially challenging concept for clinicians and certainly warrants further investigation. This finding does not in any way imply that therapy for the UL after stroke is now obsolete. 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. Therapy is also vital in reducing functional disability in those who experience residual impairment.

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 or manage basic tasks independently [40]. Early work in TMS after stroke [21-23] made the observation that patients with MEPs experienced a better recovery in the UL than those without MEPs. This may be particularly useful in patients who present clinically with severe loss of motor function. If MEPs can be elicited in their UL using TMS, this may indicate that they have the potential to recover a degree of UL function. Heald et al. [41] and Pizzi et al. [42] reported that some patients without MEPs were still able to regain some strength in the UL. It is important to note that this refers to resolution of impairment rather than recovery of function. It does, however, indicate that TMS alone is not sufficient to provide an accurate prognosis for every patient. Magnetic resonance imaging (MRI) may be useful for distinguishing between those patients without MEPs, to identify those with potential for limited recovery of movement [5].

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 prediction of individual prognosis. Therefore, they proposed an algorithm for predicting the recovery of UL function using a combination of all three (PREP algorithm). This novel sequential approach recognises that not all patients will require all assessments and begins with the simplest and cheapest assessment which can be completed by all clinicians (clinical assessment).

Previous work by Nijland et al. [17] 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, using a multivariate logistic regression model. 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 able to use the UL functionally in everyday activities. In the first step of the PREP algorithm, 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, rather than create a regression model for a group of 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 considered "safe". The SAFE score had 88% positive predictive power for a complete recovery of UL function at 12 weeks [7]. The patients who had a score of ≤ 7 underwent TMS testing to determine if they had MEPs present or not. If MEPs were present, they were predicted to have a notable recovery of UL function by 12 weeks. If MEPs were absent, they continued on to have an MRI to determine which patients still have some limited potential for recovery and which have none [7, 12].

Using the PREP algorithm, Stinear et al. [7] successfully demonstrated a method of identifying which patients require TMS as a prognostic tool after stroke. They reported that 60% of patients had TMS and only 20% required MRI. As TMS is relatively inexpensive to administer, this reflects a significant saving in expenditure when compared with the use of MRI in isolation. 40% of patients did not require TMS at all and were able to be accurately assessed with the SAFE score. As this was the first study of its kind to attempt to provide a

sequential approach to prediction of recovery, 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 have acknowledged that in this sample, there was only a small subset of severely impaired participants and more work needs to be done to refine the boundaries between the categories of limited or no potential [7].

The studies discussed here highlight two important and exciting uses of TMS in stroke which have the potential to influence clinical decision making and change the direction of therapy, making it more targeted to each individual patient: a) the use of TMS to check for the presence or absence of MEPs to predict proportional recovery of impairment, and b) the use of TMS in conjunction with clinical assessment and MRI to predict functional recovery.

The discovery of the importance of MEPs in proportional recovery of impairment after stroke raises an important issue of how patients are stratified or allocated to groups during stroke research [31]. It is becoming clear that comparing groups on baseline clinical assessment alone (such as UL strength or function) is not sufficient to ensure that both groups have equal potential for recovery at baseline. We now know that the severity of impairment early after stroke does not necessarily reflect the functional outcome at six months, and that large variation in outcome may occur *regardless* of therapy input. Therefore, it may not be possible to attribute the changes in function to the intervention performed in the research. This applies whether the intervention is pharmacological or

some form of physical therapy. For example, the researcher may unwittingly have several patients who are MEP negative in one group, while all patients in the second group are MEP positive. In this situation, the second group will perform better than the first group with or without an intervention, skewing the results of the study. The risk is that researchers will choose to exclude severely impaired patients as they are more likely to be MEP negative. This is difficult to do accurately as there is no agreed clinical level at which MEPs are guaranteed to be absent, which means all patients without movement would likely be excluded. It would be unfortunate for this to occur, as within this group of patients with no movement early after stroke, there may be some who are actually MEP positive and may make remarkable gains with physical therapy or other interventions. This discovery of the benefits of TMS to differentiate between severely impaired patients may open up opportunities for research into treatment modalities specifically suited to this patient population.

The advantages of TMS are that it is inexpensive, quick to deliver, safe, and a relatively straightforward way to test the functional integrity of the CST. It is a test that could potentially be done at the bedside by a clinical neurophysiology team in an acute clinical setting or even clinicians on the ward. However, TMS is still not a one-size-fits-all solution. It is not suited for everybody, and even after testing, more information is required for some patients. Because of this, there is still much work to be done before TMS can be implemented into standard clinical practice as a prediction tool early after stroke. Some suggestions for future research are: Increased research into TMS as a predictor in the LL, using larger sample sizes of patients; research to be carried out within the clinical setting rather than in a laboratory; a cost-benefit analysis of the potential use in clinical practice;

and assessing the feasibility of training clinical staff to perform this test. For TMS to be used as a practical rather than theoretical tool for predicting recovery of motor function after stroke, it needs to be well understood and accessible to the people who are likely to be using the results (i.e. the clinicians).

**Treatment**

TMS can also be used as a treatment adjunct to promote recovery of motor function after stroke. Unlike the single pulse TMS used in prediction studies, rTMS can be used to modulate the excitability of the motor system. Depending on the rTMS protocol used, it may either increase or decrease the excitability of the stimulated M1 [43-46]. Current research into rTMS is primarily limited to the chronic stage after stroke, with few studies investigating the use of rTMS in acute or sub-acute stroke.

The use of rTMS to modulate cortical excitability in chronic stroke is based on a model of interhemispheric inhibition (IHI) described in previous work [47-50]. This model suggests that after stroke, excitability in the ipsilesional M1 is reduced, relative to excitability in the contralesional M1. In addition to this, transcallosal inhibition from the contralesional M1 to the ipsilesional M1 is increased, which further suppresses the stroke M1 [49, 50]. This imbalance of excitability between the ipsilesional and contralesional motor cortices has been associated with poor motor outcomes [51, 52]. Repetitive TMS aims to rebalance the excitability between the cortices by increasing excitability of the ipsilesional M1 (facilitatory protocols) or reducing excitability of the contralesional M1 (inhibitory protocols) [43].

Facilitatory rTMS protocols have conventionally used high frequency rTMS to increase the excitability of the ipsilesional M1, which may improve motor function after stroke [8, 44, 53-55]. Kim et al. [55] found that a single session of 10 Hz facilitatory rTMS both increased the excitability of the ipsilesional cortex and increased dexterity, when compared with the sham TMS control protocol. Other authors have demonstrated that 3 Hz rTMS also has a facilitatory effect with effects on motor function still present 1 year after stroke [56, 57]

Another rTMS protocol aimed at increasing excitability of the ipsilesional cortex called intermittent theta-burst stimulation (iTBS) was introduced by Huang et al. [53]. This involves three pulses given at 50 Hz repeated every 200 ms. iTBS consists of 2 second bursts of pulses given at 10 second intervals. The facilitatory effect of iTBS lasts at least 15 minutes which is significantly longer than the duration of after-effects from high frequency rTMS which can be as low as 3-4 minutes [45, 53, 58]. The advantages of iTBS over high frequency rTMS are the lower stimulus intensities required and the shorter application times, making the intervention more comfortable for the participant [58].

Continuous theta-burst stimulation (cTBS) is a TBS protocol that can be used to suppress the excitability of the contralesional or unaffected hemisphere. This consists of three pulses at 50 Hz delivered every 200 ms for 20 – 40 seconds [58]. Huang et al. [53] demonstrated that cTBS produced effects which lasted over an hour after the stimulus protocol was complete. This is significantly longer than the effects of suppressive rTMS which last around 15 minutes [58]. Low frequency rTMS has also been demonstrated to have an inhibitory effect in healthy adults [46], and, when applied to the contralesional hemisphere, it suppresses the contralesional M1, therefore reducing transcallosal inhibition

to the stroke M1 [59]. Early trials demonstrated a reduction in excitability of the contralesional M1, however this neurophysiological effect did not translate into improvement in hand function in some studies [46], but did in others [59].

In a small study of 15 chronic stroke patients, Fregni et al. [60] reported that daily low frequency rTMS to the contralesional hemisphere for five days resulted in reduced excitability of the contralesional M1, and improved paretic hand function compared with the control group, with effects lasting two weeks after the completion of the treatment. In contrast, Ackerley et al. [61] found a single session of cTBS suppressing the contralesional hemisphere resulted in a deterioration in paretic hand function, suggesting that the contralesional hemisphere may play a role in the recovery of hand function after stroke in some patients, possibly via ipsilateral descending pathways [62]. These findings also indicate that the number of sessions delivered may impact on the effect of the intervention.

It is unclear whether increasing the excitability of the stroke hemisphere with facilitatory rTMS or iTBS, or suppressing the unaffected hemisphere using inhibitory rTMS or cTBS is more effective in improving motor function after stroke. Sasaki et al. [63] compared a 5 day programme of either high or low frequency rTMS in patients during the acute stage after stroke and found that high frequency facilitatory rTMS of the stroke hemisphere produced the greatest increase in recovery of motor function. However, the final assessment occurred immediately after the fifth rTMS session, with no longer term follow-up, so it is not possible to draw conclusions about longer term effects. Another study by Kedhr et al. [56] compared 1 Hz rTMS of the unaffected hemisphere (inhibitory) with 3Hz rTMS of the affected hemisphere (facilitatory) in acute stroke, and found that although both

groups displayed improved motor function, the group receiving the 1 Hz inhibitory rTMS had greater improvements in arm function three months after stroke.

One of the challenges when using rTMS as a treatment is the large variability in individual responses [64]. Cheeran et al. [65] suggest that genotype is one factor which may influence an individual's response to techniques aimed at modifying synaptic plasticity in the motor cortex. Eighteen healthy participants underwent genotyping for polymorphisms of the brain-derived neurotrophic factor gene (BDNF) before undergoing single sessions of cTBS and iTBS (one week apart). Those participants carrying the 'Met' allele of the BDNF gene displayed reduced or absent effects of both cTBS and iTBS. This implies that it is more difficult to induce neuroplastic changes in 'Met" carriers [65]. Antal et al. [66] replicated this result with a retrospective study of 15 participants. These findings need to be taken into account when considering using TBS or rTMS as a therapeutic tool in the clinical setting.

Although rTMS is considered to be a treatment adjunct alongside standard physical therapy, few studies indicate whether the participants were undergoing training at the same time as receiving the rTMS or TBS. Several studies report that patients were receiving conventional therapy, but have not specified dose or timing in relation to receiving rTMS [56, 57, 63]. Both Ackerley et al. [61] and Kim et al. [55], however, successfully used rTMS immediately prior to upper limb training as a method of "priming" or preparing the brain for therapy. This technique has potential for use in clinical practice but requires further investigation with larger sample sizes.

Ironically, although the use of rTMS as a therapeutic adjunct has received far more attention to date than TMS as a predictive tool, there are still a large number of questions to answer before it can be incorporated into routine clinical care. Most studies have been

carried out at the chronic stage after stroke (> 6 months). The critical period for beginning rehabilitation after stroke is actually within the first 30 days [67], with most patients reaching close to their maximum recovery by 3 months after stroke [68]. This disparity between the time period of rTMS research taking place and when rehabilitation takes place in the clinical setting means it is difficult to translate this technique into clinical practice. A systematic review by Stinear et al. [69] into timing of motor rehabilitation trials after stroke found only six randomised controlled trials (RCTs) of rTMS within the first 30 days after stroke.

This lack of research into rTMS in sub-acute stroke raises the question of how well these protocols can be translated into clinical practice. The IHI model of hemispheric imbalance of excitability, which rTMS protocols are based on, was originally developed in chronic stroke patients where the excitability and interactions between the stroke and unaffected hemispheres are well established. However, a novel finding by Stinear et al. [70] is that although in acute stroke the excitability of the stroke hemisphere was reduced, there was no evidence of an increased excitability of the unaffected hemisphere. And although there was a reduction of transcallosal inhibition from the stroke M1 to the unaffected M1, there was no increase in transcallosal inhibition from the unaffected M1 to the stroke M1 [70]. These findings suggest that rTMS protocols aimed at suppressing the contralesional side may be either ineffective or detrimental in the sub-acute stage after stroke.

Although rTMS research has shown modest results, there is a lack of cohesion in the current literature. A Cochrane review by Hao et al. [71] found that few conclusions could be drawn about the effectiveness of rTMS after stroke due to the heterogeneity of studies, the lack of randomised controlled trials, the small sample sizes and the lack of studies in the

sub-acute stage post-stroke. This makes it difficult to determine whether this is going to be a useful tool in stroke rehabilitation or not. Many questions need to be answered before rTMS can be implemented into routine clinical care, such as which hemisphere to target at the acute stage, what is the optimal or safe dose early after stroke, how many sessions are required and whether therapy needs to follow rTMS immediately for optimal results. For these reasons it is still too early to include rTMS into routine clinical care in the rehabilitation of the upper limb early after stroke.

**Conclusion**

There has been considerable progress in TMS research in stroke over the last few years. Of particular note are the advances in the use of TMS as a prognostic tool early after stroke and the role of TMS in identifying which patients will experience proportional recovery. These advances indicate that TMS may play an important role in providing baseline stratification of patients in future clinical trials, regardless of whether the intervention is pharmacological or a form of physical therapy. Further investigation is needed, preferably in larger clinical trials during the sub-acute stage after stroke, to identify which patients will benefit from each TMS protocol, before the use of TMS as a predictor or as a treatment can be integrated into routine stroke care.

## References

[1] WHO. The global burden of disease: 2004 update. World Health Organization. Geneva2004.

[2] Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012;125:e2-e220.

[3] Hachinski V, Donnan GA, Gorelick PB, Hacke W, Cramer SC, Kaste M, et al. Stroke: working toward a prioritized world agenda. Stroke. 2010;41:1084-99.

[4] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1:1106-7.

[5] Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. Brain. 2007;130:170-80.

[6] Talelli P, Greenwood RJ, Rothwell JC. Arm function after stroke: neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. Clin Neurophysiol. 2006;117:1641-59.

[7] Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012;135:2527-35.

[8] Di Lazzaro V, Profice P, Pilato F, Capone F, Ranieri F, Pasqualetti P, et al. Motor cortex plasticity predicts recovery in acute stroke. Cereb Cortex. 2010;20:1523-8.

[9] Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci. 2009;10:861-72.

[10] Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G, Early Prediction of Functional Outcome After Stroke I. Accuracy of physical therapists' early predictions of upper-limb function in hospital stroke units: the EPOS Study. Phys Ther. 2013;93:460-9.

[11] Kwakkel G, Wagenaar RC, Kollen BJ, Lankhorst GJ. Predicting disability in stroke - A critical review of the literature. Age and Ageing. 1996;25:479-89.

[12] Stinear C. Prediction of recovery of motor function after stroke. Lancet Neurol. 2010;9:1228-32.

[13] Bland MD, Sturmoski A, Whitson M, Connor LT, Fucetola R, Huskey T, et al. Prediction of Discharge Walking Ability From Initial Assessment in a Stroke Inpatient Rehabilitation Facility Population. Archives of Physical Medicine and Rehabilitation. 2012;93:1441-7.

[14] Kwakkel G, Kollen B. Predicting improvement in the upper paretic limb after stroke: a longitudinal prospective study. Restor Neurol Neurosci. 2007;25:453-60.

[15] Smania N, Paolucci S, Tinazzi M, Borghero A, Manganotti P, Fiaschi A, et al. Active finger extension: a simple movement predicting recovery of arm function in patients with acute stroke. Stroke. 2007;38:1088-90.

[16] Wandel A, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Prediction of walking function in stroke patients with initial lower extremity paralysis: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 2000;81:736-8.

[17] Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G, Investigators E. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: early prediction of functional outcome after stroke: the EPOS cohort study. Stroke. 2010;41:745-50.

[18] Veerbeek JM, Van Wegen EE, Harmeling-Van der Wel BC, Kwakkel G, Investigators E. Is accurate prediction of gait in nonambulatory stroke patients possible within 72 hours poststroke? The EPOS study. Neurorehabil Neural Repair. 2011;25:268-74.

[19] Patel AT, Duncan PW, Lai SM, Studenski S. The relation between impairments and functional outcomes poststroke. Arch Phys Med Rehabil. 2000;81:1357-63.

[20] Beebe JA, Lang CE. Active range of motion predicts upper extremity function 3 months after stroke. Stroke. 2009;40:1772-9.

[21] Escudero JV, Sancho J, Bautista D, Escudero M, Lopez-Trigo J. Prognostic value of motor evoked potential obtained by transcranial magnetic brain stimulation in motor function recovery in patients with acute ischemic stroke. Stroke. 1998;29:1854-9.

[22] Rapisarda G, Bastings E, de Noordhout AM, Pennisi G, Delwaide PJ. Can motor recovery in stroke patients be predicted by early transcranial magnetic stimulation? Stroke. 1996;27:2191-6.

[23] Cruz Martinez A, Tejada J, Diez Tejedor E. Motor hand recovery after stroke. Prognostic yield of early transcranial magnetic stimulation. Electromyogr Clin Neurophysiol. 1999;39:405-10.

[24] Bembenek JP, Kurczych K, Karli Nski M, Czlonkowska A. The prognostic value of motor-evoked potentials in motor recovery and functional outcome after stroke - a systematic review of the literature. Functional neurology. 2012;27:79-84.

[25] Piron L, Piccione F, Tonin P, Dam M. Clinical correlation between motor evoked potentials and gait recovery in poststroke patients. Archives of Physical Medicine and Rehabilitation. 2005;86:1874-8.

[26] Chang MC, Do KH, Chun MH. Prediction of lower limb motor outcomes based on transcranial magnetic stimulation findings in patients with an infarct of the anterior cerebral artery. Somatosens Mot Res. 2015:1-5.

[27] Hendricks HT, Pasman JW, van Limbeek J, Zwarts MJ. Motor evoked potentials of the lower extremity in predicting motor recovery and ambulation after stroke: a cohort study. Archives of Physical Medicine and Rehabilitation. 2003;84:1373-9.

[28] Terao Y, Ugawa Y. Basic mechanisms of TMS. J Clin Neurophysiol. 2002;19:322-43.

[29] Dawes H, Enzinger C, Johansen-Berg H, Bogdanovic M, Guy C, Collett J, et al. Walking performance and its recovery in chronic stroke in relation to extent of lesion overlap with the descending motor tract. Experimental brain researchExperimentelle HirnforschungExperimentation cerebrale. 2008;186:325-33.

[30] Prabhakaran S, Zarahn E, Riley C, Speizer A, Chong JY, Lazar RM, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. Neurorehabil Neural Repair. 2008;22:64-71.

[31] Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. Ann Neurol. 2015.

[32] Lang CE, Lohse KR, Birkenmeier RL. Dose and timing in neurorehabilitation: prescribing motor therapy after stroke. Curr Opin Neurol. 2015.

[33] Gladstone DJ, Danells CJ, Black SE. The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair. 2002;16:232-40.

[34] Marshall RS, Zarahn E, Alon L, Minzer B, Lazar RM, Krakauer JW. Early imaging correlates of subsequent motor recovery after stroke. Ann Neurol. 2009;65:596-602.

[35] Zarahn E, Alon L, Ryan SL, Lazar RM, Vry MS, Weiller C, et al. Prediction of motor recovery using initial impairment and fMRI 48 h poststroke. Cereb Cortex. 2011;21:2712-21.

[36] Winters C, van Wegen EE, Daffertshofer A, Kwakkel G. Generalizability of the Proportional Recovery Model for the Upper Extremity After an Ischemic Stroke. Neurorehabil Neural Repair. 2015;29:614-22.

[37] Feng W, Wang J, Chhatbar PY, Doughty C, Landsittel D, Lioutas VA, et al. Corticospinal tract lesion load - A potential imaging biomarker for stroke motor outcomes. Ann Neurol. 2015.

[38] Houwink A, Nijland RH, Geurts AC, Kwakkel G. Functional recovery of the paretic upper limb after stroke: who regains hand capacity? Arch Phys Med Rehabil. 2013;94:839-44.

[39] Xing C, Arai K, Lo EH, Hommel M. Pathophysiologic cascades in ischemic stroke. International journal of stroke : official journal of the International Stroke Society. 2012;7:378-85.

[40] Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014;9:e87987.

[41] Heald A, Bates D, Cartlidge NE, French JM, Miller S. Longitudinal study of central motor conduction time following stroke. 2. Central motor conduction measured within 72 h after stroke as a predictor of functional outcome at 12 months. Brain. 1993;116 ( Pt 6):1371-85.

[42] Pizzi A, Carrai R, Falsini C, Martini M, Verdesca S, Grippo A. Prognostic value of motor evoked potentials in motor function recovery of upper limb after stroke. Journal of Rehabilitation Medicine. 2009;41:654-60.

[43] Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol. 2006;5:708-12.

[44] Hsu WY, Cheng CH, Liao KK, Lee IH, Lin YY. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. Stroke. 2012;43:1849-57.

[45] Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain. 1994;117 ( Pt 4):847-58.

[46] Muellbacher W, Ziemann U, Boroojerdi B, Hallett M. Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. Clin Neurophysiol. 2000;111:1002-7.

[47] Duque J, Murase N, Celnik P, Hummel F, Harris-Love M, Mazzocchio R, et al. Intermanual Differences in movement-related interhemispheric inhibition. Journal of cognitive neuroscience. 2007;19:204-13.

[48] Nowak DA, Grefkes C, Ameli M, Fink GR. Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. Neurorehabil Neural Repair. 2009;23:641-56.

[49] Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. Annals of neurology. 2004;55:400-9.

[50] Cicinelli P, Pasqualetti P, Zaccagnini M, Traversa R, Oliveri M, Rossini PM. Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: a paired-pulse transcranial magnetic stimulation study. Stroke. 2003;34:2653-8.

[51] Butefisch CM, Netz J, Wessling M, Seitz RJ, Homberg V. Remote changes in cortical excitability after stroke. Brain : a journal of neurology. 2003;126:470-81.

[52] Traversa R, Cicinelli P, Pasqualetti P, Filippi M, Rossini PM. Follow-up of interhemispheric differences of motor evoked potentials from the 'affected' and 'unaffected' hemispheres in human stroke. Brain Research. 1998;803:1-8.

[53] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005;45:201-6.

[54] Talelli P, Greenwood RJ, Rothwell JC. Exploring Theta Burst Stimulation as an intervention to improve motor recovery in chronic stroke. Clin Neurophysiol. 2007;118:333-42.

[55] Kim YH, You SH, Ko MH, Park JW, Lee KH, Jang SH, et al. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. Stroke. 2006;37:1471-6.

[56] Khedr EM, Abdel-Fadeil MR, Farghali A, Qaid M. Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol. 2009;16:1323-30.

[57] Khedr EM, Etraby AE, Hemeda M, Nasef AM, Razek AA. Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. Acta Neurol Scand. 2010;121:30-7.

[58] Cardenas-Morales L, Nowak DA, Kammer T, Wolf RC, Schonfeldt-Lecuona C. Mechanisms and applications of theta-burst rTMS on the human motor cortex. Brain topography. 2010;22:294-306.

[59] Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke. 2005;36:2681-6.

[60] Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke. 2006;37:2115-22.

[61] Ackerley SJ, Stinear CM, Barber PA, Byblow WD. Combining theta burst stimulation with training after subcortical stroke. Stroke. 2010;41:1568-72.

[62] Bradnam LV, Stinear CM, Byblow WD. Ipsilateral motor pathways after stroke: Implications for noninvasive brain stimulation. Frontiers in Human Neuroscience. 2013.

[63] Sasaki N, Mizutani S, Kakuda W, Abo M. Comparison of the effects of high- and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke.

Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2013;22:413-8.

[64] Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res. 2000;133:425-30.

[65] Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol. 2008;586:5717-25.

[66] Antal A, Chaieb L, Moliadze V, Monte-Silva K, Poreisz C, Thirugnanasambandam N, et al. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. Brain Stimul. 2010;3:230-7.

[67] Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? Neurorehabil Neural Repair. 2012;26:923-31.

[68] Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76:406-12.

[69] Stinear C, Ackerley S, Byblow W. Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not: a systematic review. Stroke. 2013;44:2039-45.

[70] Stinear CM, Petoe MA, Byblow WD. Primary Motor Cortex Excitability During Recovery After Stroke: Implications for Neuromodulation. Brain Stimul. 2015.

[71] Hao Z, Wang D, Zeng Y, Liu M. Repetitive transcranial magnetic stimulation for improving function after stroke. The Cochrane database of systematic reviews. 2013;5:CD008862.