Chapter 25
The Role of TMS for Predicting Motor Recovery and Outcomes After Stroke

Cathy M. Stinear and Winston D. Byblow

Abstract Transcranial magnetic stimulation (TMS) is a safe, non-invasive technique for studying the human motor system. It can be used to evaluate primary motor cortex (M1) function after stroke, by stimulating the ipsilesional M1 and recording motor-evoked potentials (MEPs) from the paretic limbs. In this chapter, we first outline the measures of M1, intracortical and interhemispheric function that can be made with TMS. The presence or absence of MEPs is the simplest and most reliable measure that can be made with TMS. In general, patients in whom TMS can elicit MEPs from the paretic limbs make a better motor recovery and experience better functional outcomes than those patients without MEPs. We provide an overview of recent research showing that MEP status is a particularly useful biomarker for patients with initially severe motor impairment. The limitations and potential benefits of MEP status as a biomarker for patient selection in stroke rehabilitation trials are discussed.

Keywords Stroke • Motor • TMS • Prognosis • Rehabilitation

Abbreviations

AMT	Active motor threshold
CST	Corticospinal tract
ECR	Extensor carpi radialis
EMG	Electromyography

C.M. Stinear (✉)
Department of Medicine, University of Auckland,
Private Bag 92019, Auckland 1142, New Zealand
e-mail: c.stinear@auckland.ac.nz

W.D. Byblow
Department of Exercise Sciences, University of Auckland,
Private Bag 92019, Auckland 1142, New Zealand
e-mail: w.byblow@auckland.ac.nz

P.A. Lapchak, G.-Y. Yang (eds.), *Translational Research in Stroke*, Translational Medicine Research, https://doi.org/10.1007/978-981-10-5804-2_25

FM-UE	Fugl-Meyer Upper Extremity Scale
GABA	Gamma-aminobutyric acid
IHI	Interhemispheric inhibition
iSP	Ipsilateral silent period
M1	Primary motor cortex
MEP	Motor-evoked potential
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MSO	Maximum stimulator output
NPV	Negative predictive value
PLIC	Posterior limb of the internal capsule
PPV	Positive predictive value
RMT	Resting motor threshold
SAFE	Shoulder abduction finger extension
SICI	Short-latency intracortical inhibition
SP	Silent period
TMS	Transcranial magnetic stimulation

25.1 Principles of Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a safe, non-invasive and painless technique that can be used to investigate the excitability of the primary motor cortex (M1) and its descending pathways. TMS was first introduced by Barker and colleagues [1] to provide a safe and painless alternative to transcranial electrical stimulation, thus making the study of human motor cortex physiology more widely possible. With TMS a magnetic stimulus is applied via a coil (5–10 cm in diameter) through which a large but brief pulse of electrical current is passed from a high-voltage capacitor discharge system. With the coil held over the scalp, the discharge generates a brief magnetic field that induces electrical currents in the underlying tissues. These electrical currents can depolarise neurons in the cortex of the brain, causing them to fire.

A magnetic field of up to 2.5 Tesla can be generated in large circular coils. However, there is a trade-off between intensity and focality. Figure-of-eight coils consist of two smaller diameter coils wound together and provide more focal stimulation than circular coils. As well as type, size and orientation of the coil, the effects of stimulation are also dependent on whether the electrical pulse through the coil is monophasic or biphasic. Normally, coil orientation and waveform shape are set to induce posterior-anterior current in the brain which is optimal for M1 stimulation [2]. The interested reader can find further technical information, including safety procedures and contraindications for TMS, detailed elsewhere [3].

By using TMS, it is possible to probe various properties of the motor cortex and its descending pathways, including nerve conduction velocities, membrane

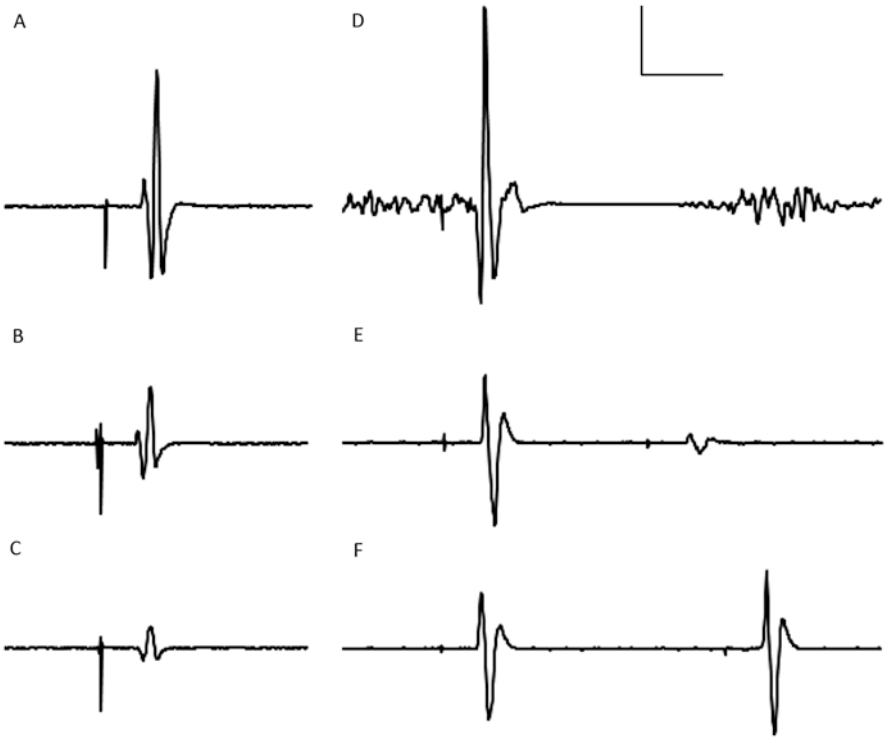

Fig. 25.1 Single- and paired-pulse TMS can be used to examine M1 cortical excitability, inhibition and disinhibition as shown in these EMG traces recorded from the first dorsal interosseous muscle. (**a)** MEP from single-pulse TMS at a stimulus intensity of 130% of RMT. (**b**, **c**) The MEP in panel (**a**) is suppressed by a subthreshold conditioning stimulus at 90% of active motor threshold delivered 2.5 ms (**b**) and 1 ms (**c**) prior to test stimulus. The decrease in MEP amplitude reflects synaptic $GABA_A$ receptor-mediated inhibition in M1 (2.5 ms) and extra-synaptic GABA-ergic tone (1 ms). (**d**) Silent period produced in the EMG trace of a preactivated muscle by single-pulse TMS at 130% RMT. The silent period reflects $GABA_B$ receptor-mediated inhibition in M1. (**e**, **f**) Suprathreshold conditioning and test stimulation (both at 130% RMT) elicit late intracortical inhibition (LICI) with an interstimulus interval of 150 ms (**e**) and late cortical disinhibition with an interstimulus interval of 250 ms (**e**) due to activation and then presynaptic inhibition of $GABA_B$-ergic neurons within M1. Calibration bars: 0.5 mV and 50 ms (Figure courtesy of Ronan Mooney)

excitability, intracortical inhibition and facilitation, interhemispheric transfer and central nervous system reorganisation. Most of these properties exhibit interesting dynamics after stroke as will be discussed below. A very brief description of the main measures of interest is provided here. Most measures are based on characteristics of the motor-evoked potential (MEP) observable in the EMG of the target muscle (Fig. 25.1). After stroke, it might not be possible to elicit a MEP due to a lesion affecting M1 itself, the descending white matter of the corticospinal tract (CST), or at the level of the brainstem. As such, the presence or absence of an MEP from TMS applied to the ipsilesional M1 early after stroke is informative about the

extent of stroke damage and recovery potential, as will be discussed in greater detail below.

Assuming MEPs can be elicited, the most common TMS measures are those which characterise the excitability of pyramidal neurons in M1 that form the CST. The MEP threshold is one such measure. Threshold depends on the excitability of neural elements including cortico-cortical axons, their synaptic contact with pyramidal neurons and the initial axon segments of the pyramidal neurons [4, 5]. The threshold can be determined with the target muscle at rest (RMT) or preactivated during slight voluntary contraction (AMT) and is defined as the minimum stimulator intensity required to consistently produce a MEP of a given amplitude (e.g. RMT = 50 uV; AMT = 100 uV; [6]). There are several methods to determine threshold including the relative frequency method, which is the most common, and adaptive methods which allow more rapid determination of threshold when using threshold tracking techniques [7]. Threshold is measured in units of stimulator output, normally expressed as a percentage of maximum (e.g. 50% MSO).

The size of the MEP (amplitude or area) for a given stimulus intensity can be used to track changes in corticospinal excitability over time. Stimulus intensity may be set relative to maximum stimulator output (e.g. 80% MSO) or threshold (e.g. 120% RMT), and stimuli are delivered at a single, optimal stimulation site. A stimulus-response curve characterises excitability by plotting MEP amplitude across a range of intensities from threshold to plateau. Although the curve is normally sigmoidal in shape, the slope of the linear region is often used as an index of corticospinal excitability [8]. In contrast, TMS mapping involves recording MEPs elicited by a constant stimulation intensity (e.g. 110% RMT) delivered at several stimulation sites. Map size (area, volume) and centre of gravity can be determined for a given muscle representation [9]. The added advantage of mapping is that it can be sensitive to shifts in representation position or area which may be evident after stroke [10]. The disadvantage is that it takes a considerable amount of time to perform, although recent advances with ‘rapid mapping’ make it more feasible for exploring spontaneous or treatment-related cortical reorganisation after stroke [11].

The cortical silent period (SP) is another measure that can be derived from single-pulse TMS, delivered while the target muscle is preactivated. This procedure involves suprathreshold TMS of the contralateral M1 (e.g. 80% MSO, 130% RMT) which is large enough to produce a period of EMG silence in the range of 150–250 ms, followed by the return of voluntary muscle activity. The duration of the SP is indicative of the excitability of $GABA_B$ receptor-mediated inhibitory function within M1 [12]. For some patients, the SP can be challenging or even impossible to obtain from stimulating the ipsilesional M1 because the patient is unable to voluntarily contract muscles on the paretic side [13].

A measure of transcallosally mediated inhibition can be obtained from suprathreshold single-pulse TMS of the M1 that is ipsilateral to the contracted muscle (iSP). The iSP is detected as a period of reduced EMG activity 30–70 ms poststimulus [14]. The iSP permits the examination of ipsilesional M1 function in more severely impaired patients, many of whom are unable to activate the paretic side

[15]. The iSP can be sensitive to post-stroke reorganisation that occurs with long-term motor practice [16].

Paired-pulse TMS is often used to investigate M1 intracortical and interhemispheric inhibition and facilitation, indicative of GABAergic and glutamatergic function within M1. Paired-pulse TMS involves delivering both a conditioning and test pulse in close succession (1–200 ms). Intracortical function can be assessed by delivering both pulses through the same coil placed over M1 and measuring the decrease or increase in size of the test MEP compared to that obtained with the test stimulus alone. Short-latency intracortical inhibition (SICI) is examined with a subthreshold conditioning stimulus and an interstimulus interval between 1 and 5 ms [17], reflecting $GABA_A$ receptor-mediated processes, which may be downregulated post-stroke [18]. Intracortical facilitation is examined with an interstimulus interval of 6–15 ms, with 10 or 15 ms intervals being most common, but this measure is not routinely investigated after stroke.

Dual-coil TMS can be used to examine interhemispheric inhibition (IHI) between M1s and provide a measure of transcallosally mediated inhibition similar to the ipsilateral SP measure. To examine IHI, each M1 is stimulated with a separate coil, delivering a suprathreshold pulse (e.g. 120% RMT). Inhibition of the test MEP is evident at short (10–15 ms) and long (40 ms) intervals, indicative of excitability of different populations of GABA receptor-mediated inhibitory neurons [19, 20].

Measures of functional connectivity between different cortical areas (e.g. premotor-motor, intrahemispheric or interhemispheric) can also be examined with dual-coil TMS. These approaches may reveal functional reorganisation after stroke [21], but to date, they have not been widely used, perhaps owing to the size of stimulating coils and difficulty in accurately targeting adjacent cortical regions.

25.2 TMS in Stroke

In general, greater interhemispheric asymmetry in measures obtained with TMS is related to worse motor performance at the time of testing, at the group level of analysis. It is well established that the ipsilesional M1 is less excitable than the contralesional M1 in patients with motor deficits after stroke [22–24]. This is reflected by higher resting and active motor thresholds, and smaller MEP amplitudes, compared to the contralesional M1 and to healthy controls [24]. As noted above, there is evidence of altered intracortical function, with reduced SICI in the ipsilesional M1 at the subacute stage of recovery [22, 24]. Conversely, studies of interhemispheric inhibition after stroke have produced more variable results. A recent meta-analysis did not detect any differences in the amount of IHI passed from the contralesional to ipsilesional M1 and vice versa nor in the amount of IHI produced by stroke patients and healthy controls [24]. Furthermore, this meta-analysis found no differences between the contralesional M1 and healthy controls on any TMS measure made at the subacute or chronic stage of stroke [24]. This indicates that the neurophysiological effects of stroke are most readily detected by TMS

measures of ipsilesional M1 excitability and SICI, rather than interhemispheric or contralesional measures. TMS measures made from muscles distal to the elbow produce very similar results [24]. The choice of target muscle is therefore less critical than using optimal TMS and EMG techniques.

As noted above, most TMS measures require a MEP to be generated, with the exception of MEP status. The use of TMS to evaluate ipsilesional M1 excitability and SICI is therefore limited to patients with a functional ipsilesional M1 and CST. In general, measurement error is lower, and reliability is higher for measures of corticospinal excitability obtained with single-pulse TMS, than for measures of intracortical function obtained with paired-pulse TMS [25–27]. This may be due to the fact that inhibition or facilitation measures are strongly affected by the test MEP amplitude, which may be compromised, or variable, or both after stroke. It remains to be determined whether paired-pulse inhibition and facilitation measures may be more reliable if obtained using modern threshold tracking techniques, which address the limitation of test MEP variability [28–30]. A further consideration is that TMS does not readily test the function of alternative descending motor pathways that may become more important for motor performance after stroke, such as the reticulospinal and rubrospinal tracts [31]. Finally, TMS can't be used with all patients due to contraindications, in the same way that not all patients can have an MRI scan. Despite these limitations, TMS can be used to make predictions for individual patients about motor recovery and outcomes after stroke. The most commonly used TMS predictor is MEP status, because it doesn't require a MEP to be generated and has good to excellent reliability [32].

25.3 TMS for Prediction After Stroke

It is important to note that we use the term 'predict' in the clinical rather than statistical sense. That is, we will discuss TMS measures made at one time point that can make a prediction about motor performance at a later time point. This is in contrast to TMS measures that are associated with motor performance at the time of testing.

TMS performed within the first few days after stroke can predict subsequent motor outcomes and motor recovery. Motor outcomes describe the level of impairment or function at a specific time point post stroke, regardless of performance immediately after the stroke. The disadvantage of measuring outcomes is that they provide no information about whether performance has improved, remained stable or deteriorated over time. This is overcome by measuring motor recovery, which is the change in motor impairment or function over time. Recovery can be quantified as the difference in a measure of motor performance between two time points, such as the difference in a clinical score obtained 1 week and 6 months after stroke. Recovery can also be expressed as a proportion of the available improvement, and this is described in further detail below.

25.3.1 Motor Outcomes

25.3.1.1 Upper Limb

The first reports of the prognostic value of MEP status at the subacute stage of stroke were published in the early 1990s. These early studies typically used MEP status as a predictor for upper limb motor outcomes and were systematically reviewed in 2002 [33]. This review of five studies including 255 patients concluded that the presence of MEPs in the paretic hand within 7 days of stroke predicted better outcomes for motor impairment and function. Motor impairment was evaluated with the Medical Research Council (MRC) grades, the Motricity Index and the Fugl-Meyer Upper Extremity (FM-UE) Scale, while function was evaluated with the Barthel Index [33]. This review also calculated odds ratios for studies with at least 50 patients and found that the odds of a good outcome for MEP+ patients ranged from 5.49 to 13.50 relative to MEP− patients.

These findings are supported by a more recent systematic review of 14 studies that included 480 patients [34]. The majority of studies evaluated MEP status in intrinsic hand muscles within 2 weeks of stroke and found that the presence of MEPs predicted better outcomes for both motor impairment and function. Motor impairment was typically evaluated with MRC grades, while function was most commonly evaluated with the Barthel Index [34]. None of the studies reviewed utilised a measure of functional outcome that was more specific to the upper limb, such as the Wolf Motor Function Test or Action Research Arm Test [35].

Positive predictive values (PPV) for MEP status range between 86% [36] and 93% [37], indicating that the presence of MEPs is a reasonably robust predictor of good upper limb motor outcome. Several authors have noted that MEP status is a particularly useful predictor for patients with initially more severe motor impairment [33, 38], with one study reporting a PPV of 100% in this subset of patients [37]. However, negative predictive values (NPV) for MEP status range between 35% [39] and 95% [38] demonstrating that the absence of MEPs does not necessarily mean a poor outcome.

MEP status primarily reflects the functional integrity of M1 and the CST and is not sensitive to the potential contributions of other areas of motor cortex and alternate descending motor pathways to motor outcomes. This may explain the lower NPV for MEP status. Patients who are initially MEP− may still have some capacity for recovery of motor output via cortical reorganisation and the upregulation of transmission via alternate ipsilesional motor pathways [31, 40, 41]. There is also some evidence for upregulation of transmission via uncrossed corticospinal projections after stroke [22]. This can be evaluated with TMS of the contralesional M1; however, the prognostic utility of ipsilateral MEPs at the subacute stage is currently unknown.

Some of the limitations of TMS as a predictor of motor outcomes can be overcome by combining TMS measures with other biomarkers. We have developed one approach to this, called the Predict Recovery Potential (PREP) algorithm [42]. This

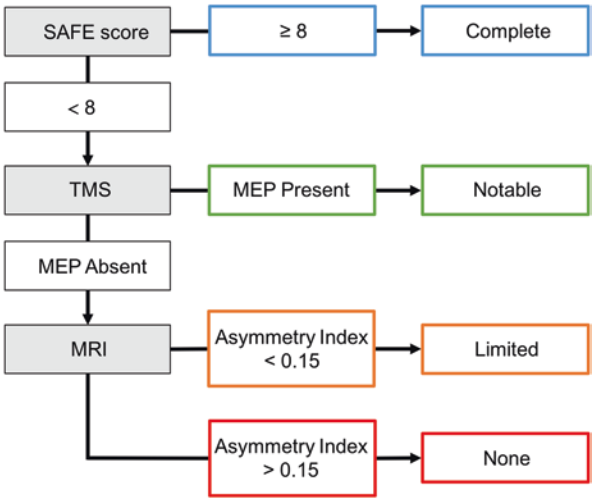

Fig. 25.2 The PREP algorithm combines clinical, TMS and MRI measures within the first few days after stroke to predict upper limb functional outcome 3 months later. The SAFE score is obtained by adding the MRC strength grades for paretic shoulder abduction and finger extension. If the score is 8 or more (out of 10) within 72 h of stroke symptom onset, the patient is likely to make a complete, or near-complete, recovery of upper limb function. If the score is less than 8 at 72 h post stroke, TMS is used to determine MEP status around 5 days post stroke. Patients in whom TMS can elicit a MEP in the paretic wrist extensors are MEP+ and are predicted to make a notable recovery of upper limb function. Patients who are MEP− proceed to an MRI scan 10–14 days post stroke. Diffusion-weighted imaging is used to calculate the mean fractional anisotropy of the posterior limbs of the internal capsules, and an asymmetry index is calculated. If the asymmetry index is <0.15, the patient is likely to have a limited recovery of upper limb function. If the asymmetry index is >0.15, the patient has essentially no potential for recovery of meaningful upper limb function (Adapted from Stinear et al. [43])

algorithm sequentially combines clinical, TMS and MRI measures to predict upper limb functional outcome for individual patients (Fig. 25.2). The PREP algorithm was initially developed with a sample of 40 first-ever ischaemic stroke patients [43] and has since been validated with a sample of 192 patients with first-ever or previous ischaemic or haemorrhagic stroke [44]. In brief, upper limb impairment is evaluated within 72 h of stroke symptom onset by grading shoulder abduction and finger extension strength with the MRC grades. The scores for each movement are summed to calculate a SAFE score out of 10. Patients with a SAFE score less than 5 at 72 h post-stroke are then assessed with TMS to determine MEP status. Those who are MEP+ are predicted to have a good functional outcome within 3 months. It should be noted that patients with a SAFE score of zero at 72 h post-stroke can be MEP+, indicating that their ipsilesional M1 and CST are functional despite their inability to produce voluntary muscle activity early after stroke. TMS is therefore essential for distinguishing between patients with initially severe motor impairment who have potential for a good motor outcome and those who do not. However, as described above, TMS of ipsilesional M1 does not evaluate all descending motor pathways,

and patients who are MEP− may still have potential for recovery of some upper limb function. For this reason, the PREP algorithm uses MRI to evaluate the structural integrity of the posterior limb of the internal capsule (PLIC). The mean fractional anisotropy is calculated for each PLIC and an asymmetry index calculated. Patients with an asymmetry index <0.15 are likely to have a limited recovery of upper limb function, while those with an asymmetry index >0.15 are likely to have none.

The PREP algorithm capitalises on the high PPV for MEP status in patients with more severe initial upper limb impairment. The algorithm overcomes the low PPV for MEP status by using MRI to evaluate stroke damage to all tracts passing through the posterior limb of the internal capsule. Sequentially combining clinical, TMS and MRI measures is more efficient than obtaining all biomarkers from all patients. TMS is only required for approximately one third of patients, and MRI is only required for approximately one half of these [44]. Using TMS to evaluate patients with a SAFE score <5 efficiently leverages the high positive predictive value of MEP status, while using MRI in MEP− patients overcomes the lower negative predictive value of MEP status.

25.3.1.2 Lower Limb

Very few studies have evaluated the usefulness of TMS in predicting lower limb motor outcomes after stroke. This may be related to the technical challenges of eliciting MEPs from lower limb motor cortex. The location, orientation and relatively smaller surface area of the lower limb M1 representation make it difficult to stimulate with TMS. A double-cone stimulating coil and higher stimulus intensities are usually required, and MEPs are typically recorded from distal muscles such as tibialis anterior and abductor hallucis brevis [45].

Two studies have evaluated MEP status in tibialis anterior early after stroke. The first study of 38 patients found that the presence of MEPs within 10 days of stroke predicted recovery of ankle dorsiflexion, but not independent walking, 6 months post-stroke [46]. In contrast, a more recent study of 14 non-ambulatory patients found that those who were MEP+ within 4 weeks of stroke were independently walking 6 months post-stroke [47]. The relevance of lower limb MEP status to functional outcomes such as walking is therefore unclear. This may reflect the higher degree of redundancy in motor control of the lower limb compared to the upper limb. Upper limb function is heavily dependent on contralateral CST function, whereas the lower limbs receive descending commands from both hemispheres, and walking function is also supported by reticulospinal projections [48]. These important differences in neuroanatomy mean that MEP status determined with TMS of ipsilesional M1 may not be a strong predictor of subsequent lower limb impairment and walking outcomes.

25.3.2 Motor Recovery

As noted above, recovery is a dynamic process captured by a measure of change. Change in impairment can be measured with the upper and lower extremity portions of the Fugl-Meyer [49], which focus primarily on the presence of unwanted motor synergies which are common after stroke [50]. Recovery from impairment captures true biological recovery, whereas improvements in function can also reflect compensatory mechanisms. Selecting appropriate measures of recovery based on an intervention's mechanisms is crucial. A long-standing view is that the failure of many clinical trials of stroke rehabilitation may relate to the choice of outcome measures rather than the lack of efficacy of the study intervention [51]. In humans, almost all recovery from motor impairment occurs within the first 3 months of stroke, emphasising a time-sensitive period for spontaneous biological processes which give rise to recovery and the time-critical nature for interventions which may interact with it [52]. The dynamics of recovery from motor impairment are explored in further detail below.

25.3.2.1 Upper Limb

The dynamics of recovery from upper limb impairment have been the topic of considerable recent investigation since an original and noteworthy observation by Prabhakarahn and colleagues [53–59]. Within the first 3–6 months after stroke, a large subset of patients recover from upper limb impairment to a fixed proportion that is almost exactly 70% of the available improvement. That is, for this subset of patients, the change in UE-FM score (ΔFM) is proportional to the initial impairment (FM_{ii}) such that $\Delta FM = \beta \cdot FM_{ii}$, with β values approximating 0.7 within 95% confidence intervals [55, 58]. This '70% rule' has been observed in over 500 patients in countries with different rehabilitation services [53–56, 59], regardless of patients' age, gender, stroke type and therapy dose [55, 56, 58].

However, not all patients fit the 70% rule. Earliest studies suggested that initial impairment may determine whether or not recovery would be proportional, but the criterion FM-UE score has varied markedly between studies [53, 54, 60]. This matter appears to have been resolved by using TMS. Single-pulse TMS applied to the ipsilesional M1 within the first 2 weeks of stroke identified those patients who would fit the 70% rule. TMS was used to determine MEP status of the paretic wrist extensor muscle, extensor carpi radialis (ECR), using stimulus intensities of up to 100% MSO if necessary [55]. MEP status more accurately predicted which patients would fit the 70% rule than measures of initial impairment. Patients with MEPs (MEP+) could achieve a proportional recovery, *regardless* of initial impairment. MEP+ patients with initial FM-UE scores as low as 4 and 5 exhibited a proportional (70%) recovery, whereas MEP− patients did not even though some had higher initial FM-UE scores [55].

Presently it is not clear why the proportion of upper limb recovery from impairment is 70%, and not some other number, nor is it clear what intervention if any may help patients exceed 70% recovery [61]. Again, measures made with TMS have shed some light on these questions. Using TMS, we measured resting motor threshold from the ECR of both upper limbs between 2 and 26 weeks after stroke. Obviously, it was only possible to obtain RMT measures from the paretic upper limb in MEP+ patients. We were interested in the recovery of ipsilesional M1 excitability and so measured change in ipsilesional RMT (ΔRMT) relative to baseline, computed at 6, 12 and 26 weeks post stroke. Initial impairment of RMT was calculated as the difference between baseline ipsilesional RMT and contralesional RMT (which was stable and normal across the entire period). A near identical proportional relationship was observed in both ΔFM and ΔRMT. Ipsilesional RMT improved by approximately 70% of the available improvement. The ΔFM and ΔRMT data from the study are shown in Fig. 25.3. The RMT finding provides some insight into the potential neurobiological mechanisms of proportional recovery and led us to propose that there may be a consistent relationship between the volume of permanently damaged corticospinal axons and the volume of temporarily dysfunctional adjacent axons. If so it may be that initial impairment measured with the FM scale captures both permanent and temporary axonal dysfunction, MEP status is sensitive to the extent of permanent axonal loss, and RMT is sensitive to the recovery of temporarily dysfunctional axons [55]. These ideas warrant further investigation.

25.3.2.2 Lower Limb

Given the ubiquitous nature of proportional upper limb recovery, a similar proportional recovery dynamic may be expressed in other domains. Little is known at present, but there has been some evidence for proportional recovery from aphasia [62]. Only one study to date has demonstrated proportional recovery from lower limb impairment [57]. This study found that all patients followed the 70% rule, regardless of tibialis anterior MEP status and despite over half of the 32 patients being non-ambulatory at baseline. The lack of predictive power for MEP status may simply reflect the technical challenges associated with stimulating the lower limb motor cortex. Or it could mean that preserved ipsilesional corticomotor function is not essential for proportional recovery from lower limb impairment since neural pathways such as the reticulospinal tract provide greater redundancy in the control of the lower limb compared to the upper limb. Interestingly, similar to the upper limb and despite greater contributions of brainstem-mediated pathways, recovery from lower limb seems to be limited to 70%, but confirmation from larger samples is required.

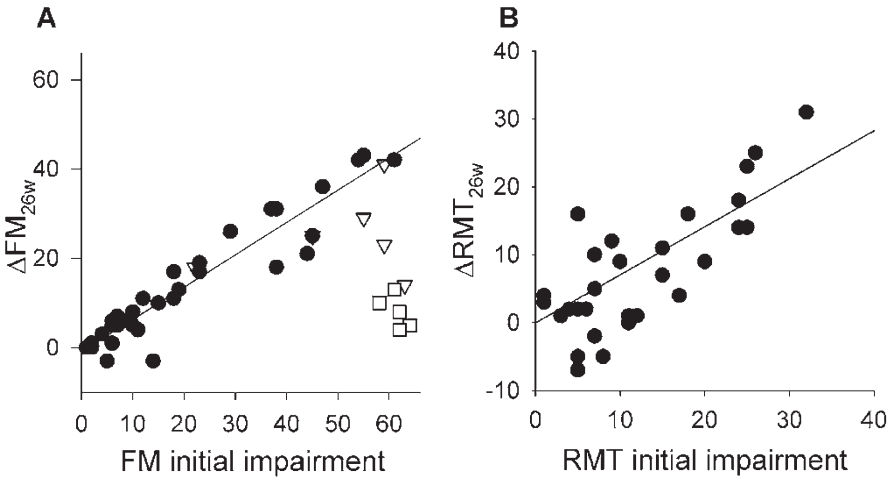

Fig. 25.3 Recovery from upper limb impairment and of ipsilesional M1 RMT is proportional to initial impairment for patients with MEPs (MEP+). (**a**) The recovery from upper limb impairment is reflected by change in FM-UE score between baseline and 26 weeks post-stroke (ΔFM_{26w}). Recovery is proportional to initial impairment, calculated as 66 minus baseline FM-UE score, for patients in whom TMS can elicit MEPs in the paretic wrist extensors (*filled circles*). The *line* represents the '70% rule'. Patients without MEPs (*open symbols*) make recovery between 0 and 70% of the available improvement (*triangles*) or make essentially no meaningful recovery (*squares*). Note that TMS is required to identify which patients with severe initial impairment will make a proportional recovery. (**b**). The recovery of ipsilesional M1 RMT is reflected by change in RMT between baseline and 26 weeks post-stroke (ΔRMT_{26w}). RMT initial impairment was calculated as the difference between ipsilesional RMT at baseline and the average contralesional RMT, which was stable. For these MEP+ patients, recovery of ipsilesional M1 RMT is proportional to initial RMT impairment, and the line represents the '70%' rule (Adapted from Byblow et al. [55])

25.3.3 TMS at the Chronic Stage

The previous section described the pivotal role that TMS can play in predicting whether a patient will experience proportional recovery at the subacute stage, when spontaneous biological recovery is evident. The logical implication of proportional recovery is that even patients who experience proportional recovery are left with some lingering impairment, precisely because motor impairment resolves incompletely, to 70% of the maximum possible. As such the majority of patients tend to benefit from goal-directed physical therapy which allows relearning presumably via mechanisms of neuroplasticity which facilitate adaptation and compensation. Recovery from motor impairment is complete at 6 months post stroke, and this time point is the most commonly accepted onset for the chronic stage. What further gains are possible at the chronic stage, and what role can TMS play in predicting responsiveness to therapy or motor practice?

In a small randomised controlled trial, we observed that MEP status was useful in determining response to daily upper limb motor practice undertaken by chronic

patients over a 1-month period. Immediately post intervention and at 1-month follow-up, patients with MEPs made larger gains on the hand and arm portion of the FM-UE assessment than patients without MEPs [63]. Subsequently other studies have also reported that patients with a functionally intact CST (having MEPs in the paretic hand or forearm) tend to make better gains in response to therapy or intervention at the chronic stage than those who do not [64, 65]. As noted in previous reviews, MEPs may reappear during recovery, but this does not always equate to clinical improvement at the chronic stage [66], and their late reappearance may have little predictive value [22, 33].

25.4 Conclusion

In light of the research described above, one can envisage several ways that TMS might contribute to translational stroke research. TMS provides researchers with a safe, non-invasive tool for evaluating motor system function in patients recovering from stroke, though it does have several limitations. Measures can be variable within subjects and over time and are more difficult to obtain for the lower limb. Furthermore, descending motor pathways other than the CST are not readily evaluated with TMS and may play important roles in both upper and lower limb recovery. Similarly, TMS sheds little light on the role of cortical areas other than M1 in recovery after stroke.

Despite these limitations, MEP status is probably the simplest and most reliable TMS measure and is a useful predictor of upper limb motor recovery and outcome. MEP status could be incorporated in the design of upper limb rehabilitation trials initiated in the first few days after stroke. Doing so would provide important information for patient selection and stratification, in addition to demographic and clinical measures already used. MEP status for patient selection could be particularly useful when recruiting patients with more severe initial motor impairment, as MEP+ patients are more likely to recover and achieve better outcomes than MEP− patients, despite similar baseline clinical scores. MEP status for patient selection might also be important in trials of interventions designed to enhance recovery from motor impairment. Matching treatment and control groups on MEP status, and therefore the potential for proportional recovery, could increase the trial's sensitivity to treatment effects. In addition to threshold measures, more sophisticated measures of intracortical and interhemispheric function may provide important mechanistic insights in longitudinal studies of motor recovery after stroke. These in turn could identify new therapeutic targets and biomarkers of treatment effects. The development of techniques to reduce the variability of TMS measures, and algorithms for combining MEP status with other biomarkers, will support greater use of TMS in stroke rehabilitation research.

References

1. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1(8437):1106–7.
2. Kaneko K, Kawai S, Fuchigami Y, Morita H, Ofuji A. The effect of current direction induced by transcranial magnetic stimulation on the corticospinal excitability in human brain. Electroencephalogr Clin Neurophysiol. 1996;101(6):478–82.
3. Pascual-Leone A. Handbook of transcranial magnetic stimulation. London: Arnold; New York: Oxford University Press; 2002.
4. Amassian VE, Cracco RQ. Human cerebral cortical responses to contralateral transcranial stimulation. Neurosurgery. 1987;20(1):148–55.
5. Di Lazzaro V, Ziemann U, Lemon R. State of the art: physiology of transcranial motor cortex stimulation. Brain Stimul. 2008;1(4):345–62.
6. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol. 2015;126(6):1071–107.
7. Huynh W, Vucic S, Krishnan AV, Lin CS, Hornberger M, Kiernan MC. Longitudinal plasticity across the neural axis in acute stroke. Neurorehabil Neural Repair. 2013;27(3):219–29.
8. Devanne H, Lavoie BA, Capaday C. Input-output properties and gain changes in the human corticospinal pathway. Exp Brain Res. 1997;114(2):329–38.
9. Wilson SA, Thickbroom GW, Mastaglia FL. Topography of excitatory and inhibitory muscle responses evoked by transcranial magnetic stimulation in the human motor cortex. Neurosci Lett. 1993;154(1–2):52–6.
10. Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. Stroke. 2000;31(6):1210–6.
11. van de Ruit M, Perenboom MJ, Grey MJ. TMS brain mapping in less than two minutes. Brain Stimul. 2015;8(2):231–9.
12. Inghilleri M, Berardelli A, Cruccu G, Manfredi M. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. J Physiol. 1993;466:521–34.
13. van Kuijk AA, Pasman JW, Geurts AC, Hendricks HT. How salient is the silent period? The role of the silent period in the prognosis of upper extremity motor recovery after severe stroke. J Clin Neurophysiol. 2005;22(1):10–24.
14. Jung P, Ziemann U. Differences of the ipsilateral silent period in small hand muscles. Muscle Nerve. 2006;34(4):431–6.
15. Harris-Love ML, Chan E, Dromerick AW, Cohen LG. Neural substrates of motor recovery in severely impaired stroke patients with hand paralysis. Neurorehabil Neural Repair. 2016;30(4):328–38.
16. Stinear CM, Barber PA, Coxon JP, Fleming MK, Byblow WD. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. Brain. 2008;131(Pt 5):1381–90.
17. Rothwell JC, Day BL, Thompson PD, Kujirai T. Short latency intracortical inhibition: one of the most popular tools in human motor neurophysiology. J Physiol. 2009;587(Pt 1):11–2.
18. Liepert J, Hamzei F, Weiller C. Lesion-induced and training-induced brain reorganization. Restor Neurol Neurosci. 2004;22(3–5):269–77.
19. Duque J, Hummel F, Celnik P, Murase N, Mazzocchio R, Cohen LG. Transcallosal inhibition in chronic subcortical stroke. NeuroImage. 2005;28(4):940–6.
20. Talelli P, Waddingham W, Ewas A, Rothwell JC, Ward NS. The effect of age on task-related modulation of interhemispheric balance. Exp Brain Res. 2008;186(1):59–66.
21. Koch G, Oliveri M, Cheeran B, Ruge D, Lo Gerfo E, Salerno S, et al. Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. Brain. 2008;131(Pt 12):3147–55.

22. Talelli P, Greenwood RJ, Rothwell JC. Arm function after stroke: neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. Clin Neurophysiol. 2006;117(8):1641–59.
23. Perez MA, Cohen LG. The corticospinal system and transcranial magnetic stimulation in stroke. Top Stroke Rehabil. 2009;16(4):254–69.
24. McDonnell MN, Stinear CM. TMS measures of motor cortex function after stroke: A meta-analysis. Brain Stimul. 2017;10(4):721–734.
25. Schambra HM, Ogden RT, Martinez-Hernandez IE, Lin X, Chang YB, Rahman A, et al. The reliability of repeated TMS measures in older adults and in patients with subacute and chronic stroke. Front Cell Neurosci. 2015;9:335.
26. Koski L, Lin JC, Wu AD, Winstein CJ. Reliability of intracortical and corticomotor excitability estimates obtained from the upper extremities in chronic stroke. Neurosci Res. 2007;58(1):19–31.
27. Liu H, Au-Yeung SS. Reliability of transcranial magnetic stimulation induced corticomotor excitability measurements for a hand muscle in healthy and chronic stroke subjects. J Neurol Sci. 2014;341(1–2):105–9.
28. Mooney RA, Cirillo J, Byblow WD. GABA and primary motor cortex inhibition in young and older adults: a multimodal reliability study. J Neurophysiol. 2017;118(1):425–433.
29. Cirillo J, Byblow WD. Threshold tracking primary motor cortex inhibition: the influence of current direction. Eur J Neurosci. 2016;44(8):2614–21.
30. Murase N, Cengiz B, Rothwell JC. Inter-individual variation in the after-effect of paired associative stimulation can be predicted from short-interval intracortical inhibition with the threshold tracking method. Brain Stimul. 2015;8(1):105–13.
31. Ruber T, Schlaug G, Lindenberg R. Compensatory role of the cortico-rubro-spinal tract in motor recovery after stroke. Neurology. 2012;79(6):515–22.
32. Hoonhorst MH, Kollen BJ, van den Berg PS, Emmelot CH, Kwakkel G. How reproducible are transcranial magnetic stimulation-induced MEPs in subacute stroke? J Clin Neurophysiol. 2014;31(6):556–62.
33. Hendricks HT, Zwarts MJ, Plat EF, van Limbeek J. Systematic review for the early prediction of motor and functional outcome after stroke by using motor-evoked potentials. Arch Phys Med Rehabil. 2002;83(9):1303–8.
34. 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. Funct Neurol. 2012;27(2):79–84.
35. Nijland R, van Wegen E, Verbunt J, van Wijk R, van Kordelaar J, Kwakkel G. A comparison of two validated tests for upper limb function after stroke: the Wolf Motor Function Test and the Action Research Arm Test. J Rehabil Med. 2010;42(7):694–6.
36. Hendricks HT, Pasman JW, van Limbeek J, Zwarts MJ. Motor evoked potentials in predicting recovery from upper extremity paralysis after acute stroke. Cerebrovasc Dis. 2003;16(3):265–71.
37. 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(9):1854–9.
38. 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. J Rehabil Med. 2009;41(8):654–60.
39. 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.
40. Lindenberg R, Zhu LL, Ruber T, Schlaug G. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. Hum Brain Mapp. 2012;33(5):1040–51.

41. Schwerin S, Dewald JP, Haztl M, Jovanovich S, Nickeas M, MacKinnon C. Ipsilateral versus contralateral cortical motor projections to a shoulder adductor in chronic hemiparetic stroke: implications for the expression of arm synergies. Exp Brain Res. 2008;185(3):509–19.
42. Stinear CM. Prediction of recovery of motor function after stroke. Lancet Neurol. 2010;9(12):1228–32.
43. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012;135(Pt 8):2527–35.
44. Stinear CM, Byblow WD, Ackerley SJ, Barber PA, Smith MC. Predicting recovery potential for individual stroke patients increases rehabilitation efficiency. Stroke. 2017;48(4):1011–9.
45. Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol. 2012;123(5):858–82.
46. 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. Arch Phys Med Rehabil. 2003;84(9):1373–9.
47. 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;32(4):249–53.
48. Jang SH, Chang CH, Lee J, Kim CS, Seo JP, Yeo SS. Functional role of the corticoreticular pathway in chronic stroke patients. Stroke. 2013;44(4):1099–104.
49. Fugl Meyer AR, Jaasko L, Leyman I. The post stroke hemiplegic patient. I. A method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13–31.
50. Brunnstrom S. Movement therapy in hemiplegia: a neurophysiological approach. New York: Harper & Row; 1970.
51. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. Stroke. 1992;23(8):1084–9.
52. Zeiler SR, Krakauer JW. The interaction between training and plasticity in the poststroke brain. Curr Opin Neurol. 2013;26(6):609–16.
53. 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(1):64–71.
54. 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(7):614–22.
55. Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. Ann Neurol. 2015;78(6):848–59.
56. Feng W, Wang J, Chhatbar PY, Doughty C, Landsittel D, Lioutas VA, et al. Corticospinal tract lesion load: an imaging biomarker for stroke motor outcomes. Ann Neurol. 2015;78(6):860–70.
57. Smith MC, Byblow WD, Barber PA, Stinear CM. Proportional recovery from lower limb motor impairment after stroke. Stroke. 2017;48(5):1400–3.
58. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. Proportional motor recovery after stroke: implications for trial design. Stroke. 2017;48(3):795–8.
59. Buch ER, Rizk S, Nicolo P, Cohen LG, Schnider A, Guggisberg AG. Predicting motor improvement after stroke with clinical assessment and diffusion tensor imaging. Neurology. 2016;86(20):1924–5.
60. 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(12):2712–21.
61. Krakauer JW, Marshall RS. The proportional recovery rule for stroke revisited. Ann Neurol. 2015;78(6):845–7.
62. Lazar RM, Minzer B, Antoniello D, Festa JR, Krakauer JW, Marshall RS. Improvement in aphasia scores after stroke is well predicted by initial severity. Stroke. 2010;41(7):1485–8.

63. 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(Pt 1):170–80.
64. Wittenberg GF, Richards LG, Jones-Lush LM, Roys SR, Gullapalli RP, Yang S, et al. Predictors and brain connectivity changes associated with arm motor function improvement from intensive practice in chronic stroke. F1000Research. 2016;5:2119.
65. Nouri S, Cramer SC. Anatomy and physiology predict response to motor cortex stimulation after stroke. Neurology. 2011;77(11):1076–83.
66. Delvaux V, Alagona G, Gerard P, De Pasqua V, Pennisi G, de Noordhout AM. Post-stroke reorganization of hand motor area: a 1-year prospective follow-up with focal transcranial magnetic stimulation. Clin Neurophysiol. 2003;114(7):1217–25.