Prediction of motor recovery after stroke: advances in biomarkers

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Stroke remains a leading cause of adult disability, and the recovery of motor function after stroke is crucial for the patient to regain independence. However, making accurate predictions of a patient's motor recovery and outcome is difficult when based on clinical assessment alone. Clinical assessment of motor impairment within a few days of stroke can help to predict subsequent recovery, while neurophysiological and neuroimaging biomarkers of corticomotor structure and function can help to predict both motor recovery and motor outcome after stroke. The combination of biomarkers can provide clinically useful information when planning the personalised rehabilitation of a patient. These biomarkers can also be used for patient selection and stratification in trials investigating rehabilitation interventions that are initiated early after stroke. Ongoing multicentre trials that incorporate motor biomarkers could help to bring their use into routine clinical practice.

Introduction

The global burden of stroke continues to grow, with stroke prevalence in 2013 almost double that in 1990.[1] Motor impairment is common after stroke and motor recovery is crucial for regaining independence.[2] Ideally, accurate prognoses for recovery after a stroke should allow clinical teams, patients, and families to optimise rehabilitation plans with realistic goals and appropriate allocation of time and resources. However, accurate prediction of the extent of an individual patient's motor recovery can be difficult for clinicians.[3] This prognostic challenge has led to a growing interest in biomarkers of motor recovery and outcomes.[4–6] These biomarkers might be useful in the initial days after a stroke to make accurate predictions, which would assist rehabilitation planning and the selection of patients for clinical trials.

Several demographic, clinical, and radiological factors can be used to predict stroke outcomes such as disability and death. These factors include stroke severity,[7–10] age,[7–12] comorbidities,[8–12] stroke lesion volume,[10,13,14] and leukoaraiosis,[10,13,15] and have been reviewed elsewhere.[16–18] The aim of this Review is to describe research into biomarkers that might predict motor recovery and motor outcomes, and assess their significance for clinical practice.

Motor biomarkers

Biomarkers can be used to predict motor recovery, motor outcomes, or both. Motor outcomes, in contrast to motor recovery, are measured at a single timepoint, and are therefore insensitive to whether the patient's motor performance has improved, remained stable, or deteriorated over time after stroke. This limitation can be addressed by evaluating motor recovery over time, which is typically measured as the absolute difference between baseline and subsequent clinical scores. Two patients can have different absolute improvements (recovery) in their motor scores on a clinical scale and achieve the same motor outcome; they can also have the same absolute improvement in their motor scores on a clinical scale and achieve different motor outcomes.

The absolute improvement in a clinical score can be expressed as a proportion or percentage of the available improvement in that score. As a hypothetical example, if a patient initially scores 10 on a scale that ranges from 0 to 50, the available improvement is 40 points. If 6 months after stroke the patient scores 30, they have gained 20 of the available 40 points and made a 50% recovery. Measuring proportional recovery enables the detection of treatment effects despite interindividual variability in absolute recoveries and outcomes. Improvement over time is likely to reflect the neurobiological processes at work during the initial weeks and months after stroke.[19] Studying recovery could therefore deepen the understanding of underlying mechanisms, and identify therapeutic targets. In clinical research, the use of measures of proportional recovery is increasing along with the assessment of the usefulness of clinical, neurophysiological, and neuroimaging biomarkers for predicting both motor recovery and motor outcomes.

Clinical measures

Several studies[20–23] and a systematic review[24] have confirmed that motor impairment assessed within a week after stroke can predict functional outcomes. In general, greater initial impairment is associated with worse functional outcomes. Motor impairment is commonly measured with the Fugl-Meyer scale, which assesses single-joint and multi-joint movement, out-of-synergy movement, digit individuation, movement speed, dysmetria, ataxia, and reflexes. The scale has a maximum score of 66 for the upper extremity and 34 for the lower extremity, with higher scores reflecting less impairment. The Fugl-Meyer scale is valid and reliable, although there is a ceiling effect on scores for patients with mild motor impairment.[25] Evidence of proportional recovery from motor impairment is accumulating. In five studies published between 2015 and 2017,[26–30] researchers measured upper limb motor impairment within 2 weeks of stroke with the upper-extremity Fugl-Meyer scale, and at 3 or 6 months after stroke. These studies confirmed the earlier observation[19,31] that most patients achieve around 70% of the available motor improvement within

3–6 months after stroke. Together, these studies have shown proportional recovery from motor impairment in over 500 patients in countries with different rehabilitation services,[26–30] regardless of patients' age, sex, stroke type, and physical therapy dose measured in minutes.[28–30] Similarly, a study of 32 patients reported 74% proportional recovery from lower-limb impairment measured with the lower-extremity Fugl-Meyer scale, regardless of therapy dose;[32] however, trials involving larger numbers of patients are required to strengthen this finding. Preliminary work has also shown that recovery from impaired communication[33,34] and visuospatial attention[34] is proportional to initial impairment, and approximately 70% of available improvement occurs within 3 months. This finding suggests that proportional recovery is a generalised phenomenon and not an artifact of the Fugl-Meyer scale.[35]

Overall, these studies[19,26–32] indicate that proportional recovery from motor impairment might reflect a ubiquitous neurobiological process, which does not seem to be meaningfully enhanced by current therapy practices. However, systematically testing whether proportional recovery occurs in the absence of rehabilitation would be unethical. Patients included in studies to date[19,26–32] have completed therapy programmes that vary widely in terms of type, intensity, and duration, but despite these large variations in therapy, for most patients their recovery from impairment remains at approximately 70% of the available improvement. This consistency in proportional recovery might mean that a basal amount of spontaneous activity and therapy is sufficient for proportional recovery to occur,[36] and that current therapy practices do not seem to increase the proportion recovered.[28,30,32] To achieve a greater proportion of motor recovery, delivery of a substantially higher dose of therapy aimed at reducing impairment might be needed.[36]

Proportional recovery typically ranges from 63% at 3 months[30] to 78% at 6 months[26] after stroke. Why the proportion is approximately 70%, and not 50% or 90%, is unclear. The precise value is perhaps less important than the existence of a proportional relationship, which suggests that limits to the biological processes responsible for recovery from impairment exist. These processes are likely to involve both structural and functional plasticity.[37] Although proportional recovery can explain motor impairment outcomes, it is less likely to explain functional outcomes because these can be improved by movement strategies that compensate for motor impairment.[38] For example, reach-to-grasp function can be improved by trunk flexion to compensate for impaired elbow extension. Furthermore, although some patients with severe initial motor impairment have proportional recovery, others do not.[19,26–30] Unfortunately, clinical scores cannot reliably discriminate between these two subgroups;[27,28] however, neurophysiological and neuroimaging biomarkers can be useful in these circumstances.

Neurophysiological biomarkers

Electroencephalography (EEG) is a well established tool in neurological practice, with several applications in the management of patients with stroke, including monitoring of cortical activity in patients who have had an acute ischaemic stroke and during carotid surgery.[39] Evidence indicates that an ipsilesional loss of power in the alpha frequency band and an increase in the delta frequency band detected within 2 weeks of stroke are linked to a poor outcome.[40] However, the outcomes are typically measured using the modified Rankin Scale, the National Institutes of Health Stroke Scale, or death as an outcome, and are therefore not specific to motor recovery or motor outcomes. Preliminary evidence showing that quantitative EEG biomarkers might predict motor recovery has been provided by a study[41] of 42 patients that recorded their resting EEGs within 3 weeks of stroke symptom onset. Coherence in the beta frequency band between the ipsilesional primary motor cortex and the rest of the cortex had a positive linear relationship with improvements in a composite score of upper-limb motor performance during the first 3 months after stroke. The potential for translation of EEG biomarker use to clinical practice is high, as EEG is already part of standard practice, and a study[42] has shown that the acquisition of EEG biomarkers is feasible in the acute stroke setting. However, further work is needed to develop automated data processing for ease of use by clinicians and to identify EEG biomarkers that can make predictions for individuals rather than identify predictors for groups of patients.

Transcranial magnetic stimulation non-invasively tests corticomotor function. A brief magnetic stimulus is delivered over the primary motor cortex to depolarise underlying neural tissue, which can produce a motor-evoked potential (MEP) recorded from contralateral muscles with surface electromyography. A systematic review[43] of 14 studies that included 480 patients found that patients in whom an MEP could be elicited within 7 days of stroke (MEP-positive patients) had better upper-limb outcomes than those who did not have an MEP within this time period (MEP-negative patients).[43] The reported positive predictive values for MEP status range between 86%[44] and 93%,[45] indicating that the presence of an MEP is a reasonably robust predictor of good upper-limb motor outcome. One study[45] of 24 patients with severe upper-limb impairment 1 week after stroke reported positive predictive values of 100% for motor impairment outcome, indicating that the presence of MEPs might be a particularly useful biomarker for this subset of patients. However, the reported negative predictive values for MEP status range between 72%[46] and 95%,[46] showing that the absence of an MEP does not rule out a good outcome.

MEP status can also help to identify which patients will have proportional recovery from upper-limb motor impairment. Patients with severe upper-limb

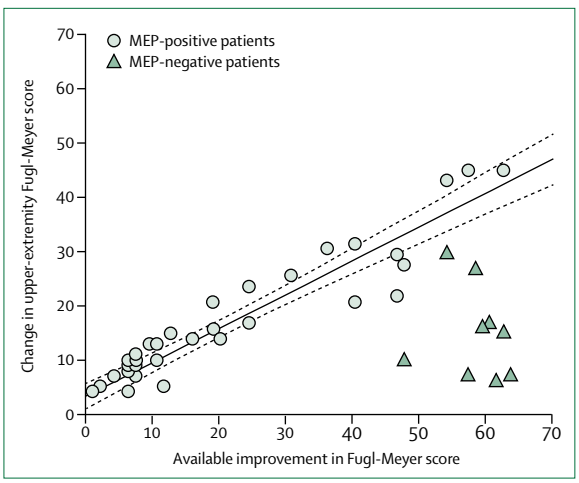

***Figure 1*: Relationship between MEP status and recovery from upper-limb motor impairment after stroke**

Recovery from baseline to 6 months after stroke is shown as change in upper-extremity Fugl-Meyer score. For MEP-positive patients, recovery is proportional to the available improvement; the regression line (with 95% CIs indicated by dashed lines) represents the relationship between available (x) and actual (y) improvement (y=0·70x). No relationship exists between available and actual improvement for MEP-negative patients. Note that two patients can have a similar initial Fugl-Meyer score of 6 points and an available improvement of 60 points. However, an MEP-positive patient is likely to recover about 70% of the available improvement, whereas an MEP-negative patient will not. MEP status is therefore a useful neurophysiological biomarker that can identify patients with initially severe impairment that will make a proportional recovery from upper-limb impairment. Reproduced from Byblow and colleagues,[28] by permission of John Wiley and Sons. MEP=motor-evoked potential.

impairment, and an upper-extremity Fugl-Meyer score as low as 6 out of 66, showed proportional recovery, provided MEPs could be recorded in their paretic wrist extensors (figure 1).[28,30] One study[28] of 48 patients also investigated corticomotor excitability in both hemispheres by determining the threshold stimulus intensity to produce an MEP. Excitability of the ipsilesional primary motor cortex is usually lower than that of the contralesional primary motor cortex soon after stroke,[47] and often increases over the following weeks and months.[48] The recovery of ipsilesional primary motor cortex excitability was also proportional to initial impairment (approximately 70%) with a time course that paralleled the recovery from motor impairment.[28] One limitation of this study[28] was that most patients (83%) had had a subcortical stroke, potentially reducing the generalisability of its findings. This limitation was partly addressed by another study[30] of 157 patients that found that 136 patients who were MEP positive proportionally recovered from upper-limb motor impairment, whereas 21 patients who were MEP negative did not. In this study[30] only 33% of patients had had a subcortical lacunar infarct, indicating that the predictive value of MEP status is probably generalisable to patients with stroke lesions affecting their cortex. Together, these findings suggest that the ipsilesional primary motor cortex supports proportional recovery from upper-limb impairment.

The potential value of lower-limb MEP status as a biomarker has received less attention and is less clear. A study[49] of 38 patients found that the presence of MEPs in the paretic tibialis anterior muscle within 10 days of stroke predicted recovery of ankle dorsiflexion, but not independent walking, 6 months after stroke. By contrast, a study[50] of 14 non-ambulatory patients found that the presence of MEPs in the paretic tibialis anterior muscle within 4 weeks of stroke identified patients who would be able to walk independently 6 months after stroke. The relevance of lower-limb MEP status to functional outcomes such as walking is therefore unclear.

To date, only one study[32] of proportional recovery from lower-limb impairment has been reported. In contrast to findings for the upper limbs, the study[32] of 32 patients found that all patients recovered proportionally (74%), regardless of tibialis anterior MEP status, and despite over half of the patients being non-ambulatory at baseline. The low predictive power for lower-limb MEP status might be a reflection of the technical challenges associated with stimulating the lower-limb motor cortex, which increase the likelihood of false negatives. Additionally, preserved ipsilesional corticomotor function might not be essential for proportional recovery from lower-limb impairment. Alternate descending pathways, such as the reticulospinal tract, and uncrossed projections from the contralesional cortex, provide greater redundancy in the control of the lower limbs than of the upper limbs.[51] Despite the possible contributions of these alternate pathways, recovery from lower-limb impairment appears to plateau around 70%, although confirmation in a larger group of patients is needed.

Overall, the accumulated evidence indicates that the presence of MEPs in the paretic upper limb soon after stroke predicts better motor recovery and outcomes. MEP status might be a particularly useful biomarker for patients with initially severe motor impairment, because it can detect functional descending motor pathways even in the absence of voluntary motor activity. This ability to detect functional descending motor pathways overcomes the limitations of clinical assessment when making motor predictions for severely impaired patients, who can have the capacity for upper-limb recovery if they are MEP positive. However, the absence of MEPs does not necessarily indicate that the patient will have a poor recovery or outcome. The relatively low negative predictive power of MEP status reflects the main limitation of transcranial magnetic stimulation, which is that testing is largely confined to primary motor cortex function and output. Transcranial magnetic stimulation cannot easily be used to test the function of areas other than the primary motor cortex, including the premotor cortex or alternate motor pathways, such as the reticulospinal and rubrospinal tracts. Neuroimaging can overcome these limitations by assessing the entire sensorimotor network.

Neuroimaging biomarkers

Several structural and functional neuroimaging biomarkers have been investigated in patients with stroke.[6,52–56] The structural integrity of cortex and white matter pathways can be assessed with T1-weighted and diffusion-weighted MRI. Diffusion-weighted MRI enables the assessment of disruption to the microstructural organisation of white matter, with measures such as fractional anisotropy and axial diffusivity.[55] In general, greater disruption of descending white matter pathways is associated with worse motor performance. For example, in a study[57] of 60 patients, researchers acquired diffusion-weighted images within 12 h of stroke symptom onset and two independent raters established whether the stroke had directly affected the ipsilesional primary motor cortex, premotor cortex, centrum semiovale, corona radiata, or posterior limb of the internal capsule. Damage to the posterior limb of the internal capsule was the best predictor of motor outcomes at 90 days after stroke, with outcome categorised as no deficit, mild-to-moderate deficit, or severe deficit, according to the motor subscale of the National Institutes of Health Stroke Scale. A subsequent study[58] of 70 patients calculated the mean fractional anisotropy asymmetry of the corticospinal tracts at the level of the pons, measured 30 days after stroke. Greater asymmetry predicted worse motor outcomes at 2 years after stroke, with outcome classified as no deficit, mild-to-moderate deficit, or severe deficit, according to the Motricity Index strength assessment score. In both of these studies,[57,58] biomarkers of white matter damage were better predictors of motor outcome than was lesion volume, which is a finding consistent with other reports.[55] However, a limitation of both studies is that they categorised motor outcome using gross tests of primarily proximal movement. Another two studies[29,59] have reported negative linear relationships between acute lesion load on the ipsilesional corticospinal tract and upper-extremity Fugl-Meyer score 3 months after stroke. One of these studies[29] also reported a lesion-load cutoff value that identified, with 100% positive predictive values, patients who would have a poor motor outcome, defined as an upper-extremity Fugl-Meyer score less than or equal to 23. These studies indicate that neuroimaging biomarkers of white matter integrity might be useful predictors of motor outcome. However, a limitation is that the biomarkers were used to predict coarse motor outcomes. More precise predictions would be useful for preparing individual patients' rehabilitation plans and when selecting patients for clinical trials.

Neuroimaging biomarkers of white matter integrity might also be useful predictors of motor recovery. Greater stroke lesion damage to the corticospinal tract results in poorer recovery from impairment that is not proportional to the initial impairment.[27,28] A study[27] of 23 patients found that greater fractional anisotropy asymmetry along the corticospinal tracts can identify patients who will not have proportional recovery from upper-limb motor impairment. Furthermore, for patients who are MEP negative, fractional anisotropy asymmetry at the posterior limbs of the internal capsules could distinguish patients who will have partial recovery from those who will have essentially no recovery of voluntary movement in their upper limbs.[28] However, larger cohorts of patients are needed to confirm these preliminary findings.

Functional MRI can provide measures of cortical activity and connectivity while patients are at rest or doing a motor task. In general, more normal patterns (ie, more similar to those seen in healthy controls) of task-related cortical activity[52–54] and resting-state functional connectivity[56,60] are related to better motor performance at the time of scanning. Functional MRI measures might also predict upper-limb motor outcomes. Two studies,[61,62] each with 21 patients, identified patterns of task-related brain activity that could predict subsequent motor outcomes. In one study,[61] patients with mild-to-severe upper-limb impairment were scanned, within a week of stroke, during a hand-grip task with their paretic upper limb. Motor outcome was a composite score based on grip strength and Action Research Arm Test score,[61] and a median split was used to categorise patients as having a good or poor outcome 4–6 months after stroke. Patients with a good motor outcome had greater activity in their ipsilesional primary motor cortex, ipsilesional premotor cortex, and contralesional cerebellum, at the acute stage than patients with poor motor outcomes. This pattern of activity correctly classified 18 (86%) of 21 patients, whereas the baseline composite motor score correctly classified 16 (76%) of 21 patients. The second study[62] scanned patients during passive movement of the paretic wrist 1 month after moderate-to-severe stroke. A multivariable regression model, including task-related cortical activity and baseline total motor Fugl-Meyer score (with a maximum of 100 points), explained 87% of the variance in the total motor Fugl-Meyer score at 6 months after stroke. Removing the baseline total motor Fugl-Meyer score increased the explained variance to 96%. These preliminary studies[61,62] indicate that patterns of both passive and active task-related brain activity measured with functional MRI might predict motor outcomes with similar, and possibly greater, predictive power than clinical scores. However, these studies are both limited by their small sample sizes, and these biomarkers require validation in larger cohorts of patients.

Neuroimaging biomarkers can overcome the main limitation of transcranial magnetic stimulation (a technique that cannot readily access the function of areas other than the primary motor cortex) by assessing the structure and function of the wider sensorimotor network, including non-primary motor cortex, sensory cortex, and the cerebellum. Together, the findings obtained by using the neuroimaging biomarkers reviewed in this section confirm the important role of the ipsilesional motor cortex and corticospinal tract in motor recovery after stroke. Measures of stroke damage to the

ipsilesional descending white matter pathways, such as fractional anisotropy or lesion load, could have cutoff values that might be used to make predictions for individual patients. Further research with larger cohorts of patients is needed to establish robust functional neuroimaging biomarkers.

Implications for clinical practice

Predicting recovery from motor impairment and functional outcomes for individual patients is a difficult[3] but crucial component of rehabilitation and discharge planning. The MEP status of patients with initially severe upper-limb impairment could be useful to differentiate between those who will make a proportional motor recovery and those who will make a poor motor recovery. Identifying severely impaired patients with the capacity for proportional recovery could help to ensure that these patients are given appropriate rehabilitation that builds on their recovery from impairment to improve their function. Predicting a patient's impairment score (eg, on the basis of initial upper-extremity Fugl-Meyer score[26–30]) is less clinically useful than predicting their motor function outcome, because their motor function outcome is more relevant to their independence in activities of daily life. Two studies[20,21] have predicted upper-limb functional outcome based on simple clinical measures, including the ability of the patient to place their paretic hand on top of their head[21] and to extend their paretic fingers.[20] The predictions in these studies were accurate, but were for coarsely dichotomised patient outcomes; one study[21] dichotomised impairment outcome at an upper-extremity Fugl-Meyer score of 32 points, and the other study[20] dichotomised functional outcome at an Action Research Arm Test score of 10 points. More precise predictions might be possible by combining biomarkers.[6,63,64] Most studies have combined demographic, clinical, and biomarker information in multivariable regression models to explain variance in motor recovery or outcome for groups of patients. However, the resulting regression equations are not particularly useful when making predictions for individual patients in clinical practice.

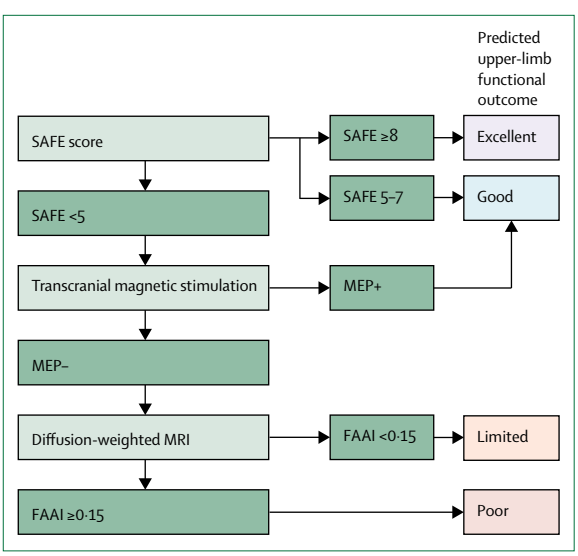

***Figure 2*: The Predict Recovery Potential algorithm to predict individual upper-limb functional outcomes for a patient after stroke**

The four outcome categories of excellent, good, limited, and poor are based on a cluster analysis of Action Research Arm Test scores 3 months after stroke, and relate to distinct levels of upper-limb use in activities of daily life.[65] The algorithm prioritises the assessment of corticomotor function over corticomotor structure. Motor output is first assessed clinically with the SAFE scale (ranging from 0 to 10), which is calculated by adding the Medical Research Council strength grades for shoulder abduction and finger extension. When initial weakness is severe 72 h after stroke symptom onset (SAFE <5), transcranial magnetic stimulation is used to test the function of the ipsilesional primary motor cortex within 7 days after stroke.[22,64,65] If MEPs can be elicited from paretic wrist extensors, the patient is deemed MEP positive (MEP+). When the patient is MEP negative (MEP–), diffusion-weighted MRI is used to assess the asymmetry in the mean fractional anisotropy of the posterior limbs of the internal capsules (FAAI). Reproduced from Stinear and colleagues,[65] by permission of Wolters Kluwer Health. FAAI=fractional anisotropy asymmetry index. MEP=motor-evoked potential. SAFE=Shoulder Abduction, Finger Extension.

To date, only one approach has combined biomarkers within the first few days after stroke to make predictions for individual patients.[22] The Predict Recovery Potential (PREP) algorithm predicts upper-limb functional outcomes by combining biomarkers in a sequential way.[22] Clinical measures are followed by neurophysiological and then neuroimaging measures to make a prognosis (figure 2). The PREP algorithm overcomes some of the limitations of making predictions based on individual clinical measures or biomarkers. Clinical assessment of patients with initially severe motor impairment is a poor predictor of recovery.[19,26–30,66] Therefore, the algorithm uses transcranial magnetic stimulation to identify the MEP status of patients with initially severe upper-limb impairment, as those who are MEP positive have potential for recovery and a good functional outcome. Although the presence of MEPs predicts a good outcome, the absence of MEPs does not always indicate a poor outcome.[22,46,65] The algorithm addresses this ambiguity by using diffusion-weighted MRI for patients who are MEP negative to study the structural integrity of all sensorimotor tracts passing through the posterior limbs of their internal capsules. The extent of damage to these pathways distinguishes patients who are MEP negative and likely to improve from those who are not. Approximately a third of patients require transcranial magnetic stimulation, and around half of these patients are MEP negative and require diffusion-weighted MRI.[65] Therefore, this sequential approach addresses some of the limitations of using a single biomarker for all patients, and is more efficient than using all biomarkers for all patients. The PREP algorithm was developed with a sample of 40 patients who had had their first ischaemic stroke,[22] and was validated in 2017[65] in an independent cohort of 192 patients, including patients who had had previous strokes or intracerebral haemorrhages. In both studies,[22,65] the algorithm made accurate predictions for

around 80% of patients. The 2017 study[65] also found that the implementation of the algorithm in clinical practice modified the content but not the dose of upper-limb therapy measured in minutes. For example, the percentage of patients predicted to have an excellent upper-limb outcome and whose therapy programme included passive upper-limb movement fell from 32% to 8%.[65] The implementation of the PREP algorithm also shortened inpatient length of stay, which was calculated as the sum of acute stroke unit and rehabilitation unit length of stay, by approximately 1 week.[65] This finding illustrates the potential value of using biomarkers to predict motor function outcomes in clinical practice, although confirmation is needed in a range of rehabilitation settings.

Given that studies to date have found no influence of therapy dose on proportional recovery from impairment, what might be the role of rehabilitation therapies? The proportional nature of recovery means that most patients will have some residual motor impairment. The role of therapy might therefore be to improve functional outcomes by helping patients to learn to adapt to, and compensate for, their impairment. Cochrane reviews[67,68] have reported that physical therapy improves recovery of motor function after stroke,[67] although more high-quality evidence for commonly used upper-limb therapies is needed.[68] The finding that higher doses of therapy, independent of when rehabilitation is initiated, are more beneficial[67] is supported by a metaregression analysis[69] of data from 30 studies, including 1750 patients, which found a small but significant positive relationship between scheduled therapy time and motor outcome. However, a subsequent study[70] with 85 patients at the chronic stage of stroke found no correlation between the dose of therapy, measured with task repetitions, and the recovery of upper-limb function assessed using the Action Research Arm Test. This study[70] highlights the importance of initiating rehabilitation early after stroke, because the initial days and weeks are a crucial period of neurobiological recovery.[37,71] This crucial period was recently shown in a study using a mouse model of stroke.[72] The authors found that a 7-day delay in post-stroke practice of a skilled reach-to-grasp task resulted in incomplete recovery of task performance. If a second stroke was then induced in the same hemisphere, and practice initiated after 1 day, task performance fully recovered to levels achieved before the first stroke. This finding in mice provides evidence that, after a stroke, there is a short period of time with favourable biological conditions that support a beneficial response to training. Higher doses of therapy appear to interact with these favourable biological conditions to enhance recovery of motor function, but not proportional recovery from impairment. Enhancing proportional recovery from impairment might require interventions that substantially differ from current therapy practices in terms of their mechanisms of action.

Implications for clinical research

Biomarkers might be useful for patient selection and stratification in clinical trials of motor rehabilitation after stroke, but to what extent are they incorporated into trial design? Rehabilitation trials with motor primary outcomes were reviewed to address this question. Since 2011, eight assessor-blind multicentre trials[73–80] of physical therapies initiated at the acute and subacute stage of stroke have analysed data from at least 100 patients (table). The strengths of these trials include the use of an active, dose-matched control intervention,[74,77,78] frequent clinical measures made on a tightly controlled timeline,[76] and reporting of usual care therapy doses.[74,75,77,78] Limitations of the trials include an absence of follow-up measures[73] and the recruitment of patients up to 3 months[78] or 6 months[75] after stroke, which introduces variability in the timing of the intervention relative to the underlying mechanisms of motor recovery. The absence of a usual-care control group in two of the trials[73,77] meant that they were unable to detect any benefit from the treatment relative to a routine clinical practice. Although all these studies[73–80] showed improvements in patients' motor performance, none found any differences in recovery or outcome between treatment and control groups. Two broad factors might have contributed to these neutral results. First, all these trials tested interventions that were variations of current therapy practices, and the treatment and control interventions might have been too similar.[85] Second, none of these studies used biomarkers of corticomotor function or structure to select patients for inclusion. As a result, the patients in the treatment and control groups might have differed in their capacity to respond to the intervention, despite the groups being matched on baseline clinical scores. Although recruiting a large cohort will probably produce groups that are balanced on key predictors and biomarkers, it does not necessarily avoid including patients for whom the intervention is ineffective. Biomarkers could allow for the selection of patients based on their capacity to respond to the biological mode of action of the intervention, increasing the statistical power of the trial to detect intervention effects.

Three double-blind placebo-controlled multicentre trials[81–83] published since 2011 have investigated the effects of drugs on motor recovery, and also recruited at least 100 patients at the subacute stage of stroke (table). The most recent of these, published in 2017,[81] found that intravenous infusion of a monoclonal antibody against myelin-associated glycoprotein within 72 h of stroke had no effect on the recovery of gait velocity between baseline and 90 days after stroke. This study stratified patients by baseline gait velocity; however, 108 (81%) of the 134 participants were non-ambulatory at baseline, and this produced a floor effect that could have reduced statistical power to detect the effect of the intervention. By contrast, the CARS trial[82] found that an intravenously administered neuropeptide preparation improved

absolute recovery of upper-limb motor function between baseline and 90 days after stroke. Similarly, the FLAME trial[83] found that orally administered fluoxetine improved absolute recovery from motor impairment between baseline and 90 days after stroke. At first glance, these results seem to indicate that the neuropeptide preparation and fluoxetine interact with the neurobiological mechanisms responsible for motor recovery; however, this interaction is still uncertain, because neither study assessed whether proportional recovery was greater for the treatment group than the control group. Furthermore, neither study used

	Sites and locations	Recruitment period after stroke	Trial duration	Participants	Age	Intervention	Control	Primary endpoint	Main results
Motor rehabilitation									
AMOBES (Yelnik et al, 2017)[79]	9 sites in France	Within 72 h	90 days	104	67 (59–77)	Intensive physical therapy for 45 min every weekday, including resistance training, sitting, and walking training, until 2 weeks after stroke or discharge from the acute stroke unit	Soft physical therapy for 20 min every weekday, including passive limb mobilisation and assistance to sit and walk, until 2 weeks after stroke or discharge from the acute stroke unit	Change in Fugl-Meyer scale score between baseline and 90 days after stroke	Fugl-Meyer scale scores increased in both groups, with no difference between groups
EVREST (Saposnik et al, 2016)[77]	11 sites in Canada, 1 site in Argentina, 1 site in Peru, 1 site in Thailand	Within 3 months	4 weeks	141	62 (13)	Ten 60 min sessions of non-immersive virtual reality exercise over 2 weeks	Ten 60 min sessions of recreational activities, such as playing cards, bingo, or ball games over 2 weeks	Time to complete six items on the Wolf Motor Function Test, grip strength, and ability to perform a card-flip task at the end of the 2 week intervention	Time to complete the Wolf Motor Function Test decreased in both groups, with no difference between groups
ICARE (Winstein et al, 2016)[78]	7 sites in the USA	Within 106 days	12 months	361	61 (13)	A structured, task-oriented training programme for the upper limb, delivered in three 60 min sessions per week for 10 weeks	Usual care delivered in three 60 min sessions per week for 10 weeks	Change in the log-transformed time score for the Wolf Motor Function Test between baseline and 12 months after stroke	Time to complete the Wolf Motor Function Test decreased in both groups, with no difference between groups
EXPLICIT (Kwakkel et al, 2016)[76]	11 sites in the Netherlands	Within 2 weeks	26 weeks	159	61 (12)	Favourable prognosis (n=58): 60 min per day of modified constraint-induced movement therapy, 5 days per week for 3 weeks; unfavourable prognosis (n=101): 60 min per day of electromyography-triggered neuromuscular stimulation of the finger extensors, 5 days per week for 3 weeks	Usual care delivered 30 min per day, 5 days per week for 3 weeks	Time course of the Action Research Arm Test score modelled over 5, 8, 12, and 26 weeks after stroke	Action Research Arm Test scores increased in all groups, although they increased more for patients with a favourable prognosis in the intervention group than those in the control group up to 8 weeks after stroke; however, this difference in improvement was not sustained, and no differences were seen between the intervention and control groups at 12 and 26 weeks after stroke
SIRRACT (Dorsch et al, 2015)[73]	4 sites in the USA, 2 sites in New Zealand, 2 sites in Spain, and 1 site each in Egypt, Italy, India, Japan, Nigeria, South Korea, Taiwan, Turkey	Within 5 weeks	22 days (14–33)	151	63 (14)	Standardised verbal feedback about walking speed after a timed 10 m walk performed three times per week, and standardised visual feedback in the form of activity graphs constructed from wireless inertial-sensor data, delivered three times per week	Standardised verbal feedback about walking speed after a timed 10 m walk performed three times per week	Average time spent walking daily measured by wireless inertial sensors and the fastest safe walking speed over 15 m upon discharge from rehabilitation	Fastest safe walking speed increased in both groups, with no difference between groups; average time spent walking daily was stable over time with no difference between groups
CIRCIT (English et al, 2015)[75]	5 sites in Australia	Within 197 days	6 months	283	70 (3)	Circuit-class therapy delivered in a group setting up to 3 h per day, 5 days per week, or usual care for 7 days per week	Usual care	6 min walk test at 4 weeks after randomisation	The distance walked in 6 min increased in all groups, with no difference between groups

(Table continues on next page)

	Sites and locations	Recruitment period after stroke	Trial duration	Participants	Age	Intervention	Control	Primary endpoint	Main results
(Continued from previous page)									
Acupuncture (Zhu et al, 2013)[80]	4 sites in China	Within 30 days	6 months	188	66 (10)	Usual care with traditional Chinese acupuncture delivered 5 days per week for 4 weeks, and then 2 or 3 days per week for 8 weeks	Usual care	Fugl-Meyer score at 1, 3, and 6 months after randomisation	Fugl-Meyer scores increased in both groups, with no difference between groups
LEAPS (Duncan et al, 2011)[74]	6 sites in the USA	Within 2 months	12 months	408	62 (12)	Treadmill training with bodyweight support beginning 2 months or 6 months after stroke, for 36 sessions of 90 min completed in 12–16 weeks, in addition to usual care	Home exercise programme of 36 sessions of 90 min duration completed in 12–16 weeks, in addition to usual care	Proportion of patients with improved walking function at 12 months after stroke	52% of patients improved their walking function, with no difference between groups
Pharmacology									
Monoclonal antibody *vs* placebo (Cramer et al, 2017)[81]	5 sites in the USA, 5 sites in Canada, 8 sites in the UK, 12 sites in Germany	Within 72 h	180 days	134	68 (12)	Two intravenous infusions of a monoclonal antibody to myelin-associated glycoprotein (GSK249320)	Two intravenous infusions of a placebo	Change in gait velocity from baseline to 90 days after stroke	Gait velocity improved in both groups with no difference between groups
CARS (Muresanu et al, 2016)[82]	Sites in Poland, Romania, and Ukraine*	Within 72 h	90 days	208	64 (10)	30 mL of a neuropeptide mix and 70 mL of saline administered intravenously once per day for 21 days and standardised usual care	100 mL of saline administered intravenously once per day for 21 days and standardised usual care	Change in Action Research Arm Test score between baseline and 90 days after stroke	Action Research Arm Test scores increased in both groups, with a greater increase in the intervention group than in the placebo group
FLAME (Chollet et al, 2011)[83]	9 sites in France	Within 10 days	90 days	118	65 (12)	20 mg of fluoxetine administered orally once per day for 90 days and usual care	Placebo administered orally once per day for 90 days and usual care	Change in Fugl-Meyer scale score between baseline and the end of the 90-day treatment period	Fugl-Meyer scale scores increased in both groups, with a greater increase in the intervention group than in the placebo group
Neuromodulation									
EVEREST (Levy et al, 2016)[84]	21 sites in the USA	At least 4 months	30 weeks	164	56 (11)	Electrical epidural stimulation delivered over the ipsilesional primary motor cortex during 65 h of upper-limb rehabilitation distributed over 6 weeks	65 h of upper-limb rehabilitation distributed over 6 weeks	The proportion of patients in each group that improved their upper-extremity Fugl-Meyer score by at least 4·5 points, and Arm Motor Ability Test score by at least 0·21 points, measured between baseline and 4 weeks after rehabilitation	32% of patients in the intervention group and 29% of patients in the control group achieved the primary endpoint, with no difference between groups

Data are mean (SD) or median (IQR). The trials of motor rehabilitation therapies and pharmacological interventions included patients within less than 6 months after stroke, whereas the trial of neuromodulation included some patients more than 6 months after stroke. All of these trials showed improvements in motor performance, but only two pharmacological trials showed a difference between intervention and control groups. *Number of sites not specified.

Table: **Multicentre, randomised controlled trials of interventions for patients after stroke with motor impairment or motor function as the primary endpoint**

biomarkers of ipsilesional corticomotor integrity for patient selection or stratification. Therefore, more patients in the treatment groups could have made a proportional—rather than a poor—recovery than in the control groups.

Biomarkers could also be important for trials done at the chronic stage of stroke. The EVEREST trial[84] investigated the effects of electrical epidural stimulation in a single-blind randomised controlled study (table). Patients at the chronic stage completed 6 weeks of upper-limb rehabilitation and stimulation was delivered to the ipsilesional primary motor cortex of patients in the intervention group during therapy sessions. Although no differences were seen in patients' motor outcomes between the intervention and control groups, post-hoc analyses found that the intervention was more efficacious for patients in whom electrical stimulation could elicit a motor response in the paretic upper limb than in patients without a motor response,[84,86] and in those with less structural damage to the corticospinal tract.[86] No differences in baseline clinical measures were observed between patients who responded to the intervention and

those who did not.[86] These findings illustrate the potential importance of using appropriate neurophysiological and neuroimaging biomarkers in the selection of patients for motor rehabilitation trials.

Neurophysiological and neuroimaging measures are not uncommon in ongoing motor rehabilitation trials (appendix). Of 193 registered motor rehabilitation trials that are currently recruiting patients, 86 (45%) include transcranial magnetic stimulation and 42 (22%) include MRI in their protocols, illustrating that these techniques are readily used in stroke rehabilitation research. However, for patient selection, only six (3%) of these trials are using MEP status (NCT02565199, NCT02892097, NCT02779218, NCT03086551, NCT02393651, and NCT02565407), and only one is using an MRI measure (NCT01894802). The full potential of these techniques is therefore not being realised. If biomarkers are used to select and stratify patients in a clinical trial of an intervention, and the intervention is found to be effective, then implementing the intervention in clinical practice will require use of the same biomarkers to select patients for treatment. Therefore, the use of biomarkers in clinical research is likely to drive the use of biomarkers in clinical practice.

See Online for appendix

Conclusions and future directions

Interest in clinical, neurophysiological, and neuroimaging biomarkers of motor recovery and outcomes after stroke is growing,[4–6] and this Review has described some important developments in this area. These developments include the verification of proportional recovery from motor impairment in several patient cohorts, indicating that proportional recovery might reflect the underlying biological mechanisms of recovery. Accumulated evidence also supports MEP status as a useful biomarker for predicting upper-limb motor recovery and outcomes, but the usefulness of this biomarker for lower-limb predictions is still unclear. Neuroimaging biomarkers of corticomotor tract integrity can also predict motor outcomes, although currently no consensus regarding the optimal neuroimaging measure exists.

Most rehabilitation is delivered within the first 30 days after stroke, yet less than 10% of motor rehabilitation trials are initiated during this time.[87] Initiating clinical trials early after stroke is therefore important to build the evidence base for rehabilitation practice,[87] and modelling studies have shown that doing so can reduce the required sample size.[88] However, trials initiated within the first few days after stroke are complicated by several factors, including difficulty in detecting intervention effects against the background of recovery occurring at this time.[87] Sensitivity to treatment effects could be increased by ensuring that the treatment and control interventions are substantially different,[85] and by using biomarkers such as those described in this Review to select and stratify patients. The statistical power of trials designed to enhance the neurobiological mechanisms of recovery could also be increased by measuring proportional recovery from impairment.[19,26–34] Interventions that convert a poor recovery to a proportional recovery, or increase a proportional recovery to above approximately 70%, will reduce residual impairment and could allow patients to achieve better functional outcomes. Trials of such interventions for the upper limbs will need to select patients on the basis of their MEP status, because this biomarker distinguishes between patients who will make a proportional recovery and those who will not with greater accuracy than clinical measures.[28,30]

The potential clinical utility of biomarkers is supported by the findings of the first study[65] to use them in a clinical setting to guide rehabilitation of individual patients. Rehabilitation efficiency was improved; however, this improvement needs to be independently substantiated in larger cohorts in a variety of rehabilitation settings. Future studies could also investigate whether predictions based on biomarkers are beneficial for rehabilitation of the lower limbs, and for other domains such as attention and communication. Large multicentre trials incorporating biomarkers of motor recovery and motor outcomes are needed to establish their sensitivity and specificity, and bring them into routine trial design and clinical practice.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed for articles published from Sept 1, 2010, to July 1, 2017. I used combinations of the terms "human", "stroke", "cerebrovascular accident", "motor", "recovery", "outcome", "predict", "prognosis", "biomarker", "rehabilitation", and "randomised controlled trial", and applied no language restrictions. I also identified articles through searches of my own files. The final reference list was selected on the basis of originality and topical relevance.

Declaration of interests

The author developed the Predict Recovery Potential algorithm with collaborators. The author declares no other competing interests.

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