Prediction of recovery of motor function after stroke

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Background Stroke is a leading cause of disability. The ability to live independently after stroke depends largely on the reduction of motor impairment and the recovery of motor function. Accurate prediction of motor recovery assists rehabilitation planning and supports realistic goal setting by clinicians and patients. Initial impairment is negatively related to degree of recovery, but inter-individual variability makes accurate prediction difficult. Neuroimaging and neurophysiological assessments can be used to measure the extent of stroke damage to the motor system and predict subsequent recovery of function, but these techniques are not yet used routinely.

Recent developments The use of motor impairment scores and neuroimaging has been refined by two recent studies in which these investigations were used at multiple time points early after stroke. Voluntary finger extension and shoulder abduction within 5 days of stroke predicted subsequent recovery of upper-limb function. Diffusion-weighted imaging within 7 days detected the effects of stroke on caudal motor pathways and was predictive of lasting motor impairment. Thus, investigations done soon after stroke had good prognostic value. The potential prognostic value of cortical activation and neural plasticity has been explored for the first time by two recent studies. Functional MRI detected a pattern of cortical activation at the acute stage that was related to subsequent reduction in motor impairment. Transcranial magnetic stimulation enabled measurement of neural plasticity in the primary motor cortex, which was related to subsequent disability. These studies open interesting new lines of enquiry.

Where next? The accuracy of prediction might be increased by taking into account the motor system’s capacity for functional reorganisation in response to therapy, in addition to the extent of stroke-related damage. Improved prognostic accuracy could also be gained by combining simple tests of motor impairment with neuroimaging, genotyping, and neurophysiological assessment of neural plasticity. The development of algorithms to guide the sequential combinations of these assessments could also further increase accuracy, in addition to improving rehabilitation planning and outcomes.

Introduction Stroke is the third most frequent cause of death and the most common cause of acquired adult disability in developed countries. Motor impairment is a frequent complication after stroke, and is an important contributory factor to a patient’s ability to live independently. Decisions on the type, duration, and goals of rehabilitation are based on several factors, including estimates of the patient’s potential for recovery of motor function, and have far-reaching consequences. Improvements in the accuracy of prognosis for the recovery of independence in daily activities would enable realistic goal-setting and efficient resource allocation by clinicians and patients.

The degree of motor impairment is the simplest indicator of prognosis, with greater initial impairment predicting worse functional recovery. For example, voluntary shoulder and finger movements and leg motor power 7 days after stroke are strongly related to subsequent recovery of upper-limb function and gait, respectively. Notable inter-individual variability in the relation between initial impairment and subsequent recovery of function, however, means that accurate prognosis for each patient remains difficult (figure 1).

Advances in neuroimaging with MRI and in non-invasive brain stimulation with transcranial magnetic stimulation (TMS) have provided new ways to visualise and understand the anatomical and functional changes in the motor system at given time points during the course of recovery. Motor impairment at the subacute and chronic stages of recovery is clearly related to lesion location, the structural integrity of descending white matter pathways, and cortical activation at rest and during voluntary movement. TMS can be used to focally stimulate the primary motor cortex (M1) and eliciting motor evoked potentials (MEPs) in target muscles of the contralateral limb. The presence (and latency and amplitude) or absence of MEPs are measurements of the functional integrity and excitability of the corticomotor pathway, which are related to motor impairment at the time of testing. Studies of the upper limb show that ipsilesional corticomotor excitability is typically reduced after stroke, and recovery of motor function is associated with a return to balanced corticomotor excitability in the two hemispheres. The few studies of lower-limb impairment have yielded mixed results.

Use of MRI and TMS to assess the integrity of the corticomotor pathway can also assist with prediction of the patient’s motor recovery. When directly compared, the prognostic accuracy of TMS is similar to that of motor impairment assessment for the upper limb, and might be better when initial paresis is severe. Assessment of the integrity of the corticomotor pathway, however, is not yet used routinely to make a prognosis, but there have been some interesting recent developments in this area.

Motor impairment scores

The sensitivity and specificity of voluntary finger extension and shoulder abduction as prognostic...
indicators have been assessed at multiple early time points by Nijland and colleagues. On the basis of findings in 156 patients, they reported that if both of these movements could be made within 72 h of stroke, there was a 98% probability of the patient recovering at least some manual dexterity within 6 months. If neither movement could be made within 72 h, the probability of recovering some dexterity within 6 months was 25%, falling to 14% if neither movement was possible 5 days after stroke. The use of multiple assessment time points showed that accurate positive predictions can be made within 72 h, and that the accuracy of negative predictions plateaus within 5 days. This information could aid rehabilitation planning, which typically takes place within this time frame. A limitation of these findings, however, is that patients were classified as having recovered some dexterity if they scored at least 10 points on the action research arm test. This test has a maximum score of 57 and, therefore, a score of 10 does not reflect a meaningful recovery of function. Some patients probably also had scores of 10 or higher at baseline, and could have been classified as having some recovery at 6 months, when in reality their score had not changed. Nonetheless, this study demonstrates the value of assessing the predictive power of simple measures at multiple time points.

Neuroimaging

DeVetten and co-workers have recently reported the prognostic value of MRI when used at multiple early time points. In 20 patients, apparent diffusion coefficient maps were calculated from diffusion-weighted images acquired within 6 h and at 12 h, 24 h, and 7 days after stroke. Custom software was used to calculate signal intensity within regions of interest at three levels of the descending corticospinal tract, between the cervicomedullary junction and upper midbrain. These values were correlated with National Institutes of Health stroke scale (NIHSS) motor scores 3 months after stroke, with poor recovery being defined as scores higher than 2 for both the arm and leg. Poor recovery was strongly predicted by a decrease in apparent diffusion coefficient signal in the ipsilesional cerebral peduncle that peaked 7 days after stroke; the positive predictive value was 0.8 and the negative predictive value was 0.92. The apparent diffusion coefficient maps can be readily constructed from diffusion-weighted images included in a routine clinical series, and a decrease in signal can be reliably detected visually by neuroradiologists within 1 week of stroke. This study was, however, limited by a small sample size, and the NIHSS motor scores are not especially sensitive tests of limb impairment and do not reflect recovery of function. Further work is needed, therefore, to verify this approach.

Another advance in MRI is reported by Marshall and colleagues, who used functional MRI in 23 patients to assess cortical activity within 48 h of stroke. They showed...
Rapid Review

applications beyond the detection of MEPs and mechanisms. These findings indicate that TMS has excitability, possibly owing to common neural plasticity effects of theta-burst stimulation on corticomotor recovery at 6 months was strongly predicted by the modified Rankin scale (0 or >0, respectively).

Intermittent theta-burst stimulation was delivered to healthy adults. Variations in genotype could, therefore, account neural plasticity and the capacity for functional reorganisation within the motor system.

Figure 2: Suggested sequence of tests to predict recovery of motor function in patients with subacute stroke

Predicted recovery of upper-limb function refers to recovery in the weeks after stroke. Although this particular algorithm requires validation, it illustrates a potentially efficient progression from simple to more complex predictive measures, which might be a useful direction for future research. SAFE=sum of the shoulder abduction and finger extension Medical Research Council muscle grades 72 h after stroke. TMS=transcranial magnetic stimulation. MEP=motor evoked potentials in affected upper limb. Asymmetry index=asymmetry index of fractional anisotropy in the posterior limbs of the internal capsules measured with diffusion-weighted MRI.15

a correlation between these data and motor impairment 3 months later. Thus, this study showed a relation between cortical activity in the acute phase and motor impairment at a later point in recovery rather than at the time of scanning. Although assessment of functional MRI as a prognostic indicator in individual patients was not the intention of these researchers, the findings suggest that this method could eventually inform or contribute to rehabilitation decisions if technological advances decrease the complexity of analysis.

Neurophysiological assessments

The prognostic accuracy of neurophysiological assessments has been extended by Di Lazzaro and colleagues,30 who used a repetitive TMS protocol to induce neural plasticity in M1 within 10 days of stroke in 17 patients. The protocol, known as intermittent theta-burst stimulation, can temporarily increase corticomotor excitability via mechanisms of synaptic plasticity.31 Intermittent theta-burst stimulation was delivered to ipsilesional M1, and a composite value of its immediate effects on the excitability of ipsilesional and contralesional M1 was calculated. Recovery of independence in daily activities was classified as complete or partial, according to the modified Rankin scale (0 or >0, respectively). Recovery at 6 months was strongly predicted by the effects of theta-burst stimulation on corticomotor excitability, possibly owing to common neural plasticity mechanisms. These findings indicate that TMS has applications beyond the detection of MEPs and assessment of corticomotor excitability. The use of the intermittent theta-burst stimulation protocol to measure plasticity in ipsilesional M1, however, is limited to patients with detectable MEPs in the paretic upper limb. Additionally, this study did not include a sham intervention, and the usefulness of the composite ipsilesional and contralesional value remains to be validated by other studies. Despite these limitations and the small sample size, this study represents an important new concept in prognostic assessment that takes into account neural plasticity and the capacity for functional reorganisation within the motor system.

Conclusions and future directions

The studies described above share some general limitations. First, the prognostic accuracy of the assessments was not confirmed with independent datasets. Second, the neuroimaging and neurophysiology studies did not compare the sensitivity or specificity of the new prognostic assessments with those of established clinical assessments. Finally, like most studies in this area, patients received so-called standard care, which is highly heterogeneous. Therapy type and dose are potential sources of variability that could be usefully included in predictive models. This approach could be particularly important in studies of the prognostic accuracy of motor impairment scores; if a rehabilitation plan is based largely on initial impairment, the degree of that impairment can lead to the outlook becoming a self-fulfilling prophecy. For instance, severely impaired patients not expected to make a good recovery might receive less intensive therapy than patients with less initial impairment, even in controlled trials where so-called standard care is delivered. Future trials should report therapy dose to improve understanding of the relation between initial impairment and recovery of motor function.

The capacity of the individual patient’s brain to recover motor function through neural plasticity should be considered. Genetic factors can strongly affect neural plasticity; for instance, common polymorphisms of the gene for brain-derived neurotrophic factor (BDNF) decrease neural plasticity20,33 and motor learning25 in healthy adults. Variations in genotype could, therefore, have important roles in recovery.26 The cost of genotyping has decreased exponentially since the human genome project, which is opening up the possibility of screening to assist with making a prognosis and rehabilitation planning.

The development of algorithms to guide the order of assessments is likely to improve predictive accuracy for motor function recovery.26 Findings so far suggest that the first tests should be those that are quick and simple, such as bedside tests of motor impairment, with progression to more complex tests if uncertainty remains (figure 2). Later tests could include neurophysiological and neuroimaging assessments of motor system integrity and genetic testing.
These approaches need to be compared with tests of motor impairment to establish accuracy and relative and combined prognostic usefulness, and to find out whether they can be used to predict individuals’ responses to standard and new rehabilitation techniques.

Various new techniques might be useful to improve the efficacy of rehabilitation. For instance, neuro-modulation techniques, such as repetitive TMS and transcranial direct current stimulation, are being used to improve the brain’s plastic response to therapy.16–18 The prediction of which patients are most likely to benefit from these adjuvants to therapy will be essential before they can become part of clinical practice.

The recovery of motor function after stroke is difficult to predict for individual patients. Methods used to make these predictions need to be simple and inexpensive. Recent studies of impairment and early motor pathway degeneration meet these criteria and also define when these measures should be used.27,28 The potential prognostic value of cortical activity and neural plasticity measures has been explored,19,20 but more studies are needed to clarify whether they are useful, feasible, and cost-effective. Further advances will enable selection of appropriate motor rehabilitation strategies for individual patients on the basis of the integrity of the motor system and its capacity for functional reorganisation.

Conflicts of interest
I declare that I have no conflicts of interest.

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