TRANSCRANIAL MAGNETIC STIMULATION AND STROKE: A REVIEW

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## ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADM</td>
<td>abductor digiti minimi</td>
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<tr>
<td>APB</td>
<td>abductor pollicus brevis</td>
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<td>BB</td>
<td>biceps brachii</td>
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<td>BOLD</td>
<td>blood oxygenation level dependent</td>
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<td>CIT</td>
<td>constraint-induced therapy</td>
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<td>CMCT</td>
<td>central motor conduction time</td>
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<tr>
<td>cTBS(IH)</td>
<td>inhibitory theta burst stimulation over intact hemisphere</td>
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<td>DH</td>
<td>damaged hemisphere</td>
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<td>ET</td>
<td>excitation threshold</td>
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<td>FDI</td>
<td>first dorsal interosseus</td>
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<tr>
<td>fMRI</td>
<td>focal magnetic resonance imaging</td>
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<tr>
<td>Hz</td>
<td>hertz</td>
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<tr>
<td>ICF</td>
<td>intracortical facilitation</td>
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<td>ICI</td>
<td>intracortical inhibition</td>
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<tr>
<td>IHI</td>
<td>interhemispheric inhibition</td>
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<td>iTBS(SH)</td>
<td>excitatory theta burst stimulation over stroke hemisphere</td>
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<td>MEP</td>
<td>motor evoked potential</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>ms</td>
<td>millisecond</td>
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<tr>
<td>MT</td>
<td>motor threshold</td>
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<tr>
<td>PAS</td>
<td>paired associative stimulation</td>
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<tr>
<td>rTMS</td>
<td>repetitive transcranial magnetic stimulation</td>
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<tr>
<td>RSD</td>
<td>reflex sympathetic dystrophy</td>
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<tr>
<td>SEP</td>
<td>somatosensory evoked potential</td>
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<tr>
<td>SP</td>
<td>silent period</td>
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<tr>
<td>TCI</td>
<td>transcallosal inhibition</td>
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<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
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<tr>
<td>TMS</td>
<td>transcranial magnetic stimulation</td>
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<tr>
<td>UH</td>
<td>undamaged hemisphere</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<td>WHO</td>
<td>World Health Organization</td>
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SECTION 1 INTRODUCTION TO STROKE

1.1 What is Stroke?

During stroke, an interruption to all or part of the brain’s blood supply, with the subsequent deprivation of oxygen and glucose to the affected area, causes the rapid loss of brain function through the destruction of neuronal function and the initiation of an ischaemic cascade that seriously damages or kills neurones. This in turn leads to a cerebral infarction – an area of dead brain tissue.

Strokes are classified according to two major stroke categories: ischaemic and haemorrhagic strokes. Ischaemic strokes may be caused by embolism, thrombosis or systemic hypoperfusion. Haemorrhagic strokes may be intracerebral, subarachnoid, subdural or epidural in type. Ischaemic strokes are the most common, accounting for approximately 80% of all strokes. If the effects of stroke last only a few hours then this is known as a transient ischaemic attack (TIA) or mini-stroke. These types of attack occur when the interruption to the brain’s blood supply is transitory.

1.2 Symptoms of Stroke

The main symptoms associated with stroke are facial weakness and paralysis, weakness in the arm or leg, problems with speech and a loss in visual field. These symptoms may last only a few hours and disappear completely within 24 hours, as with TIAs, but even under these circumstances, immediate medical assistance should be sought, as this will help minimise damage to the brain and help prevent progression to larger, more serious episodes of stroke.

1.3 Consequences of Stroke

Stroke can result in lasting neurological damage or may even cause death unless it is diagnosed and treated promptly. Indeed, its impact is so great that it is now the greatest cause of adult disability and the third greatest cause of death in industrialised Europe and the USA.

In general, strokes affect only the regional areas of the brain perfused by the affected artery, although haemorrhagic strokes can affect local areas and also be responsible for more global symptoms caused by bleeding and an increase in intracranial pressure. Symptoms, including weakness, clumsiness, paralysis or stiff muscles and joints, usually affect only the side of the body on the opposite side to the brain damage (depending on which part of the brain is affected). Around 50% of people find it difficult to swallow following stroke, which could lead to choking if food or liquid enters the trachea as opposed to the oesophagus. In human terms, a stroke affects far more people than the affected individual only. When the stroke is severe, the patient often faces a prolonged stay in hospital and, following their discharge and depending on the severity of the consequences, constant care. This care is either provided by a family member or, in the most severe cases, by a nursing home. Frustration is evident in even those individuals suffering from a mild attack when functions, such as sentence composition, or the choice or
articulation of a desired word, are sufficiently impaired to have an impact on day-to-day life. A common complaint is that although stroke is defined as a serious medical emergency, diagnosis or treatment often does not reflect it. Following a stroke, the carers often find themselves with no knowledge or lacking the skills to care for a survivor at home and therefore have to look for information and seek guidance during this trying time. Great changes are brought about in the home situation and, often, the survivor’s character and personality, and the carer has to adapt to these. Often, alternative methods of income have to be sought as the carer seeks to arrange a working life around the care of the stroke survivor. Carers are often left feeling that their age, health, skills and abilities are not taken into account when a stroke survivor is released from hospital and that they are abandoned once the survivor has left the hospital.

1.4 Risk Factors

Several things may increase the likelihood of suffering from stroke, amongst them high blood pressure, old age, gender, diabetes, smoking, high cholesterol levels, atrial fibrillation, a previous stroke or TIA, thrombophilia and migraine with aura.

1.4.1 Age

Old age increases the risk of suffering a stroke. Most people affected by this condition are 65 years old or older, although anyone can have a stroke, including babies and children. In the UK, almost one man in every four and one woman in every five aged 45 is expected to suffer a stroke by age 85.

1.4.2 Gender

Gender has a very big effect on stroke outcome. According to the Nursing Matters Fact Sheet (USA), female stroke fatalities are proportionately greater than male stroke fatalities (11% and 8.4%, respectively) despite comparable stroke rates. Meanwhile, in developing countries, nearly 50% of all female deaths at age 50 or more are caused by heart disease and stroke. It is also known that men who survive a stroke have a slightly better expected outcome than female survivors.

1.5 Diagnosis

Tests used to diagnose stroke include: checking of blood pressure levels, since stroke can cause them to rise significantly; electrocardiograms to check heart function; blood tests to check cholesterol, clotting and blood sugar levels; brain scans, including computed tomography and magnetic resonance imaging (MRI) scans; and the swallow test, as many stroke patients have difficulty in swallowing. Tests used later on in disease progression to determine the extent of the damage include carotid Doppler tests, echocardiograms and chest x-rays. The World Health Organisation (WHO) has developed an international stroke surveillance system: STEPS-Stroke. This system allows standardisation of definitions and will help facilitate the comparison of stroke occurrence in a particular country over time, and will also allow comparisons of stroke occurrence between the populations of many countries.
1.6 Treatment and Rehabilitation

It is vital that the individual who has suffered a stroke receives medical attention as rapidly as possible, as this increases the likelihood of making a full or partial recovery, and can even save lives. Following the stabilisation of the patient, a stroke team will create an individual rehabilitation programme designed around a patient’s particular needs. Rehabilitation can help an individual to regain as much independence as possible, allowing the patient to relearn lost skills, learn new skills and discover ways to manage any permanent disabilities. Rehabilitation treatments include physiotherapy, occupational therapy, speech and language therapy, and vision correction.

1.7 Stroke and Transcranial Magnetic Stimulation

Since the 1990s, many researchers have concentrated on the potential uses of transcranial magnetic stimulation (TMS) in stroke. The potential uses postulated have included: using TMS as a method of predicting recovery from stroke; as an adjunctive, enhancing treatment prior to physiotherapy; as a treatment in its own right to improve the patient’s feeling, movement control and language skills through influencing the brain’s plasticity, responsiveness or excitability.
SECTION 2  CLINICAL EVALUATION WITH TRANSCRANIAL MAGNETIC STIMULATION

2.1 Using Transcranial Magnetic Stimulation to Map the Brain Following Stroke

As TMS may be used to elucidate brain function, researchers have seized upon it as a means of studying the diseased brain. Firstly, the technique is used to demonstrate treatment effectiveness. For example, Park et al (2004) mapped the cortical areas of stroke patients undergoing rehabilitation with TMS. The resulting map demonstrated the effectiveness of constraint-induced therapy (CIT).

Secondly, the technique is used to map brain function within the stroke-damaged brain. When this is undertaken, TMS may be used alone or in combination with other methods. In one study, TMS was employed to investigate cortico-lingual and cortico-orofacial tract function in dysarthric patients following hemispheric stroke. Delayed or absent responses were considered abnormal. Transcranial magnetic stimulation was also used by Bastings et al (2002) to evaluate the relationship between size and location of cortical motor areas and the post-stroke outcome of 12 stroke patients. This was achieved by recording motor evoked potentials (MEPs) from both hands at the same time, whilst also calculating lesion surface area, the centre of gravity and the weighted surface area.

A significant correlation was discovered between motor output and the size and weight of the affected area. The authors also concluded that preservation of cortical motor output area to the affected hand is associated with good motor function outcome, thus making this method useful for stroke prediction also.

In 2006, Cicinelli et al used focal TMS to map cortical representation via the abductor digiti minimi (ADM) muscle of the damaged hemisphere (DH) and the undamaged hemisphere (UH) at rest and during motor imagery and voluntary contraction. This study was undertaken in post-acute hemiparetic stroke patients. During imagery, the ADM map area and volume was enhanced in both hemispheres thus allowing partial correction of abnormal asymmetry between UH and DH output at rest. Imagery-induced changes in excitability were specific for the ‘prime mover’ for imagined muscle movement, but no differences were detected for the locations of stroke lesions. The authors concluded that using focal TMS to map cortical excitability changes with short-term plasticity allows motor imagery to be used as a ‘cortical reservoir’ during post-stroke motor rehabilitation. Meanwhile, Malcolm et al (2006) set out to prove whether TMS was a reliable measure of motor cortex organisation and plasticity. Motor threshold (MT), map topography and stimulus-response curves were calculated for 20 healthy individuals, tested twice over 2 weeks. Values were obtained for the abductor pollicus brevis (APB), extensor digitorum communis, first dorsal interosseous (FDI) and flexor carpi radialis muscles.

The authors concluded that the parameter results for these four muscles were moderate to good, and that TMS-assessed motor representation location, size and excitability were generally...
reliable as measures of motor system plasticity, although reliability can vary depending on the muscle assessed \(^4\).

In 2003, Foltys et al. \(^{26}\) used focal MRI (fMRI) and TMS to map brain activation patterns in patients with good and rapid recovery following stroke. The fMRI revealed that even in rapid and nearly complete motor recovery increased activity was seen in bilateral motor areas during brain activation. Impaired motor outputs were revealed by TMS, although no ipsilateral motor pathways were demonstrated \(^{26}\). In another study \(^{28}\), two complementary methods were used to assess cortical reorganisation during rehabilitation treatment following chronic stroke. The authors combined BOLD- (blood oxygenation level dependent) fMRI with paired-pulse TMS and measured cortical reorganisation both before and after CIT.

The authors demonstrated that use of the inverse dynamic process that exists between both assessment methods, where fMRI assesses activation and TMS determines intracortical excitability, during the rehabilitation period proves the value of combining methods in order to understand brain reorganisation \(^{28}\).
SECTION 3  DIAGNOSTIC TECHNIQUES

3.1  Diagnosis and the Response to Transcranial Magnetic Stimulation

It is possible to use TMS to predict stroke recovery by analysing the evoked responses. The relationship is usually directly correlated.

Turton et al (1996) 20 explored the relationship between hand and arm motor recovery and the response to TMS seen in the deltoid, biceps, extensor digitorum communis and FDI muscles. Twenty-one patients were examined, in the first instance, within 5 weeks of stroke occurrence, followed by examinations at regular periods over the next 12 months. Group A patients consisted of those who recovered quickly and who responded to TMS in all the muscles examined, even at the first test. Group B consisted of patients who recovered slowly and incompletely and initially did not respond in all the muscles tested. In patients from this group who could later activate hand muscles, the responses returned at or just before reaching this stage of motor recovery. The latencies of the responses were originally long; any decrease in length was highly correlated with returning muscle strength and hand function test scores. Ipsilateral responses from the UH were seen in hand muscles and were indicative of stroke damage, being more prevalent in the poorly recovered patients 20. Pennisi et al (1999) 52 showed that all stroke patients with complete hand palsy who responded to TMS on the affected side 1 year post-stroke, also presented with some hand motor recovery. The authors concluded that TMS is of use in indicating motor recovery but that it cannot predict global functional improvement when useful hand motor recovery is not present. During the first 48 hours post-stroke, no response to TMS is indicative of absent or very poor hand motor recovery with no functional motor function 52.

In most stroke patients, any responses to weak TMS applied only over the premotor areas and not over primary motor regions, and which are seen in the upper limb muscles ipsilateral to the DH and are of short latency, indicate the presence of deep infarcts. Although these responses did not seem to have a direct effect on recovery at six months, they were positively correlated with better bimanual coordination scores at six months 2.

Changes to interhemispheric inhibition (IHI) in the APB muscle were examined using paired TMS. Stimuli were delivered whilst the affected APB was activated or at rest, and also whilst the non-affected APB was activated or at rest. No modulation was seen to IHI in the non-affected APB of stroke patients during voluntary activation of the affected APB and, in addition, there were no changes seen to IHI during bilateral muscle activation. The IHI is asymmetrical between the hemispheres, but only when the affected muscle is at rest. The ability to modulate IHI during unilateral muscle activation is impaired in stroke patients 38.

In 2006, Wagner et al 22 created a computer-based human model study. The currents induced by TMS are perturbed in brains damaged by chronic stroke and as a result their electrical and anatomical structures are changed. Currents induced by TMS during stimulation near lesion sites are significantly changed from the norm. In addition to this, the magnitude, orientation and location of the distributions of current density are modified 22.
3.2 Motor Evoked Potentials and Central Motor Conduction Time

Through the use of MEPs and central motor conduction time (CMCT), it is possible to predict motor recovery from the effects of stroke. Most of the research into TMS and stroke has concentrated on this field – an overview of current research, arranged by year, follows.

Stimulation of 22 patients with acute stroke showed that CMCT was prolonged in only one of these patients. The prolongation was associated with poor recovery. The MEPs were absent or reduced in 11 of the patients; 10 of these patients made a poor recovery. In the remaining 11 patients, MEPs and CMCTs were within normal limits; all of these patients made a good recovery. A significant increase was seen in MEP amplitudes in those patients who improved clinically, but not in those patients who made a poor recovery. It was concluded that magnetic stimulation could be of clinical use when ascertaining the prognosis following stroke, but would also have a use when monitoring progress during recovery.

Cortical MEPs were detected from the APB muscle in 41 stroke patients. Significant differences were seen between the MEP latencies and amplitudes, and the CMCT and interside differences of bilateral CMCT of stroke patients and of healthy individuals. A statistical correlation existed between the degree of motor weakness and the severity of cortical MEP findings. Patients whose stroke stemmed from haemorrhage rather than infarction had a greater rate of abnormal MEPs. There was a complete absence of MEPs in all patients (n=4) with infarction in the middle cerebral artery territory (whether cortical or subcortical). A good correlation was seen between the damage caused and the clinical motor deficit.

Heald et al (1993) examined CMCTs in 118 stroke patients immediately following stroke in order to establish whether this would allow motor outcome and mortality to be predicted at 1-year. Patients recruited within 12-72 hours of stroke onset were divided into 3 groups: normal CMCT; delayed CMCT; and no response. In the first week post-stroke, the absence of responses in the no response group was closely correlated with symptoms and with the neurological observations of abnormal tendon reflexes and muscle tone. Those with normal CMCT scored consistently higher during the 12-month follow-up period and had a correspondingly better functional recovery; patients with no responses performed poorly during functional and neurological tests during this same period. Neurological and functional scores displayed by patients with delayed CMCT fell between those shown by the other two groups but, ultimately, outcome at 1-year was similar to the normal group. It was also seen that those with an abnormally high stimulation threshold had poor functional outcomes. Mortality was highest in the no responses group.

Twenty-seven patients were evaluated within the first seven days after acute stroke and also at three and six months post-stroke. During evaluation, MEPs were recorded bilaterally from the APB and tibialis anterior muscles. No MEPs were detected in 63% of patients; these patients had worse clinical scores than those in whom MEPs were elicited. No significant differences were seen for motor function between patients during the follow-up periods, however.

Sixty acute ischaemic sylvian stroke patients were examined using TMS; the excitation threshold (ET) was evaluated. Mean ET values were recorded at days 7, 30 and 90 post-stroke (D_7, D_30 and D_90) from two distal upper limb muscles. The development of ET differed according to the
ultimate functional outcome, with mean values being increased at D7, although values were lower at D30 and D90 in those patients with good recovery than in those with poor functional recovery. The ET values trended downwards until D30 in all patients; this effect was more noticeable in patients who recovered between D30 and D90. Lesion location had no significant effects on ET values. 

During 1996, Rapisarda et al. found that ischaemic stroke patients with preserved MEPs of over 5% MMAX on the affected side coupled with complete hand palsy had a very significant chance of recovering motor function of that hand. Where it was not possible to evoke MEPs, or the only MEPs evoked were less than 5% MMAX, the association was one of poor motor prognosis, at least after two weeks. In this particular study, assessing the amplitudes of MEPs at day one proved more useful in predicting motor outcome than the clinical scales used. The team also postulated that the presence of MEP amplitudes of >5% MMAX was of more use in prognostication than CMCT. 

The prognostic value of MEPs and somatosensory evoked potentials (SEPs) were determined for 50 patients with acute middle cerebral artery infarction; MEPs and SEPs were measured 4 days, 6 weeks and 3 months post-stroke. All parameters used were correlated to the clinical outcome and each parameter had its prognostic significance determined. When predicting the outcomes of stroke, MEPs, SEPs and age were of value when used in conjunction with a clinical scale. Only MEPs and age contributed to clinical outcome in stepwise regression analyses when combined with clinical scales. Patients with normal or delayed MEPs, measured within four days of infarction, had better outcomes than patients with no MEPs. 

Seven patients with isolated hemicerebellar lesions had their CMCTs evaluated by TMS. The CMCTs were significantly prolonged when stimulation was contralateral to the DH than it was when caused by ipsilateral stimulation; prolonged CMCT were positively correlated with the severity of motor function damage. 

D’Olhaberriague et al. (1997) evaluated the usefulness of MEPs in ischaemic stroke. They also studied the relationship between abnormalities in MEPs and infarction topography. Fifty ischaemic stroke patients were followed for up to a year, with MEPs being recorded at days 1, 3, 30 and 90 post-stroke; amplitudes and latencies/CMCTs of MEPs were measured in the hypothenar, biceps brachialis, gastrocnemius and quadriceps muscles. Patients who scored 1-3 on the Rankin scale at 1-year had shorter latency MEPs than patients who scored 4-5 on the Rankin scale, or patients who had died during the first year post-stroke. Using MEP values in conjunction with clinical values increased correct classification from 76% to 84%. 

Hendricks et al. (1997) recorded MEPs and SEPs from 29 first-ever stroke patients whose infarct was located in the territory of the middle cerebral artery. All patients were paralysed in the upper extremity. A significant association was discovered between the presence of evoked potentials early after stroke and motor recovery. 

Motor cortical output to the ADM muscle in 15 nonhemispheric stroke patients was mapped using focal TMS and MEP evaluation. The patients were approximately 2 months post-stroke. The MEPs from the ADM muscle were recorded following focal TMS of the DH and UH at the beginning of the study (T1), and after 8-10 weeks of neurorehabilitation (T2). The MEP
threshold was significantly greater in the DH of stroke patients than in the UH of stroke patients or in healthy individuals. There was no significant difference between MEP thresholds in the UH and healthy individuals. The MEP latencies were significantly delayed in the DH during T1 and T2; a significant decrease of extenuation in motor output area was seen in ADM muscle in the DH during T1, but not in the UH or healthy individuals. This area was significantly enlarged during T2. The MEP amplitudes derived from the UH both at rest and during voluntary contractions were significantly lower than normal during T1. These amplitudes were increased during T2 when at rest, but were still lower than normal during voluntary muscle contraction. It was also discovered that CMCT was prolonged during T1 and T2. These data were correlated with clinical improvement of motor performance improvement and disability scores.

In 1998, Cruz-Martínez et al. discovered a correlation between CMCT, MEP amplitude and threshold intensity with hand motor function recovery post-stroke. The inhibitory period in the upper paretic limbs of patients with spasticity was significantly shorter than in the normal limb. This shortening was correlated to the degree of spasticity.

Also in 1998, Escudero et al. invoked MEPs in stroke patients. They discovered that poor prognosis was not as consistently related to the severity of paralysis at the time of stroke as it was to other indicators such as sphincter incontinence, having had a previous stroke, low functional scores on admission, or perceptive and cognitive losses. Evoking MEPs associated with normal or delayed CMCTs allowed the researchers to differentiate patients who had a high probability of survival and good functional recovery. Patients with no MEPs or with MEPs with no associated CMCTs had a poor likelihood of recovery or an increased risk of dying because of their stroke. Patients who initially showed no MEPs but who recovered well also showed a reappearance of MEPs during recovery. The researchers concluded that MEPs obtained by TMS are a useful method of early prognosis for motor function recovery in ischaemic stroke patients.

Focal TMS was used in both the DH and UH to examine MEPs in the affected hands of 17 monohemispheric patients in the subacute stage. The MEPs were recorded 2 (T1) and 4 (T2) months post-stroke. During T1, relaxed MEPs were smaller in the DH than in the UH and healthy individuals. During T2, DH relaxed MEP amplitudes were greater than in healthy individuals and were combined with improved clinical and functional scores. Contracted MEP amplitudes in the DH during T1 were also greater than in healthy individuals. These levels decreased toward normal levels by T2 when MEP amplitudes in the DH improved, but a further increase was seen where no MEPs were elicited by TMS of the DH. It was concluded that recovery of DH threshold excitability is a good predictive marker for hand motor function recovery.

Twenty patients had their MEPs bilaterally recorded over the thenar eminence muscles during the first days post-stroke. A comparison of threshold intensities, CMCTs and MEP amplitudes between the DH and UH was also undertaken. The patients were re-examined after 6 months. It was concluded that during the first few days post-stroke, MEPs recorded at rest or during voluntary muscle contraction are of use in the prognosis of stroke outcome, as patients who show early response to TMS regained good motor function during the following months. Any electrophysiological improvement is closely related to hand motor function recovery.
Feys et al (2000) measured whether MEPs or SEPs are a reliable measure of future recovery. In acute stroke, only 1 out of 50 of the patients tested had a normal response to TMS, while responses to TMS were completely absent in 74% of all the patients. Even 2 months after initial testing, normal MEP responses were seen in only 2 of the 50 patients. They concluded that not being able to evoke MEPs or SEPs within a patient was an indication of poor recovery, but that neurophysiological measures alone were not sufficient in predicting motor recovery. When these measures were combined with clinical examination, however, a clear benefit in predicting outcome was gained.

Thirty-eight first time unilateral cortical or subcortical stroke patients had their CMCT values studied. It was discovered that MEP amplitude and CMCT were correlated with the percentage change in recovery score as measured three months post-stroke. Recovery of muscle strength was strongly correlated with MEP amplitude.

Motor responses evoked by TMS of the ipsilateral and contralateral motor cortex were evaluated in the affected and unaffected thenar muscles of 21 acute stroke patients. Responses in the DH and UH were absent in 10 of the patients evaluated; motor recovery was poor in these patients and was directly related to the size of the MEPs on the undamaged side. A further 5 patients had MEPs which were greater in the undamaged motor cortex than the damaged cortex; in these patients motor recovery was good. The MEPs in the affected muscles of the remaining 6 patients were greater than in the unaffected muscles; these patients also displayed good motor recovery. It was concluded that eliciting MEPs early on in acute stroke is useful in predicting motor recovery in acute stroke patients.

One hundred patients with one-sided functionally-affecting hemiparesis caused by stroke were investigated for MEPs obtained from the anterior tibial muscle four or more weeks following stroke onset and following eight weeks of inpatient rehabilitation treatment. The results were correlated with motor deficit, activities of daily living and with walking ability. Where MEP abilities were preserved, there was a greater probability that patients would regain independence in stair climbing and walking. These patients also tended to achieve higher scores on global outcome scales.

The use of TMS as a method of predicting development of reflex sympathetic dystrophy (RSD) post-stroke was evaluated. Twenty stroke patients undergoing rehabilitation had the MEPs of the affected side measured. A good correlation existed between MEPs and the Motricity Index, although there was a significant difference between MEPs and Enjalbert scores. Despite there being no significant relationship between upper-limb impairment and intensity of RSD 10 weeks post-stroke, MEPs allowed categorisation of the patients according to the differing Enjalbert scores seen 1-2 months later following full development of RSD.

The reorganisation of motor maps following vascular mono-hemispheric lesions was investigated using TMS. It was demonstrated that several specific MEP patterns were discernable in 19 stroke patients. These patterns were caused by changes to the excitability of motor cortical areas seen during chronic recovery processes. It is suggested that greater emphasis should be placed on determining handedness, and that TMS may be of use when considering specific rehabilitation regimes following stroke.
Motor cortex excitatory responses and inhibition were examined in 20 hemiparetic ischaemic stroke patients following TMS. The stroke was located in the middle cerebral artery territory 24 hours following onset. These parameters were compared with MEPs. The CMCTs were abnormal in 2 patients, but decreased ipsilateral cortico-cortical inhibition was seen in all patients following stimulation of the ischaemic cortex. Duration of the silent period (SP) was prolonged in 15 patients; resting thresholds were abnormal in 8 patients. Only the abnormal resting thresholds were consistently associated with poor motor recovery. It was concluded that motor cortex threshold measurements provide a good measurement of poor prognosis. In 40 patients with pure motor stroke, MEPs were recorded from the FDI muscle, 6 months or more post-stroke. It was discovered that MEP amplitudes, CMCTs and MTs of the DH differed significantly from those of the UH and of healthy individuals. These parameters were significantly correlated with the clinical values seen for the affected hand – 86% of patients with persistent deficits in hand strength had abnormal MEPs. In those patients who recovered completely (n=21), a significant decrease in MEP amplitude and an increase in MT was seen in the DH.

Thickbroom et al (2002) measured MEP amplitudes and thresholds in 23 patients who had suffered a subcortical ischaemic stroke up to 23 years previously. Values were obtained for both the DH and UH. It was discovered that a correlation existed between MEP amplitude and threshold, and with strength, but that no significant correlation existed between motor dexterity and with MEP amplitude and threshold.

Paired-pulse TMS stimulation of the motor cortex in stroke patients revealed changes to intracortical facilitation (ICF) and inhibition (ICI) in the DH and UH. Interrhemitic differences between the ICI and ICF slopes of healthy individuals follow a nearly identical time course in both hemispheres. These slopes differed significantly between the DH and UH in stroke patients, with ICI being decreased in the DH and normal in the UH. The authors concluded that this could be used both as a parameter in the prediction of stroke recovery and during the follow-up of patients with monohemispheric stroke.

Dachy et al (2003) investigated whether paired TMS at rest in stroke patients was a better predictor than single TMS during facilitation. Fifty-six stroke patients with single ischaemic lesions and with no electromyographic responses evoked by single TMS in the resting affected hand were evaluated 32 days post-stroke. This assessment consisted of single stimulation during contralateral hand grip and elbow flexion followed by a paired-pulse stimulation made at rest. They were further evaluated at 26 and 76 days post-stroke. During facilitation, 37% of patients responded to single TMS; these patients presented with better clinical scores at both evaluations and a better recovery. During paired TMS, 54% of patients responded; scores had increased by the second evaluation for these patients and they also had a better chance of clinical recovery. All patients that responded to single TMS also responded to the paired TMS protocol.

Patients who had suffered a first ischaemic stroke in the middle cerebral artery territory and who all had severe hand palsy at onset were evaluated for MT and MEP amplitude in the DH and UH at days 1, 8, 30, 90, 180 and 360 post-stroke. Where the damaged motor cortex was excitable at day 1, there was no significant differences between the MT in the DH and UH; they were also similar to those seen in individuals without stroke damage. It was therefore concluded that the
persistence of MEPs on the damaged side on day 1 is a reliable predictor of good motor recovery, thus confirming that TMS is of use in predicting outcome in stroke.\(^2\)

Fast corticospinal functions, analysed by MEP, were used as the base measure of motor recovery in 55 acute stroke patients with upper or lower extremity paralysis. The MEPs were evoked in the ADM, vastus medialis, biceps brachii (BB) and tibialis anterior within 10 and 40 days of stroke onset. Motor performance was also evaluated at days 10 and 40 and at 26 weeks post-stroke. Where a response was present at day 10, recovery was fast and obvious. More MEPs were evoked at day 40 than at day 10.\(^3\)

Hendricks et al (2003)\(^4\) assessed MEPs for prognostic value in hand and arm motor recovery in patients with acute stroke and total paralysis of their upper extremity. The MEPs were measured 10 days post-stroke in the BB and ADM muscles. Of the 40 patients examined, 14 presented with motor recovery of the arm. It was discovered that prognostic models could be extrapolated for recovery of both hand and arm motor recovery based on BB MEPs. It was concluded that MEPs allowed motor recovery of the upper extremity to be predicted in patients presenting with initial paralysis.\(^5\)

Also in 2003, Stulin et al\(^6\) investigated MEPs in 52 patients with stroke, 29 of which had good functional outcomes from the acute period and 23 of which had poor functional outcomes. The MEP latencies increased following stimulation of the projection of the motor area of the cortex in the DH and following spinal cord stimulation. Values for CMCTs also increased in the DH, whilst negative correlations existed between the severity of the neurological defect coupled with CMCT, and also with the motor cortex latencies on the side of the hemispheric stroke.\(^7\)

The prognostic value of early MEPs, when combined with other clinical variables, was evaluated during the acute phase in 19 patients who had first-ever stroke in the middle cerebral artery territory and also hand palsy at stroke onset. Combining MEPs with the National Institutes of Health Stroke Scale score yielded useful information for predicting hand motor outcome where initial hand palsy is present.\(^4\)

Twenty-seven single cerebral infarction patients with affected movement in either hand were studied at less than 10 days, at 1 month and at 6 months post-stroke. Patients with subcortical stroke presented with increased paired-pulse inhibition when compared with healthy individuals. Paired-pulse facilitation was also increased after cortical stroke. The location of the stroke affected inhibition time course; subcortical stroke initially increased inhibition and then decreased over time, but cortical stroke did not significantly affect inhibition although it had a more immediate and lasting effect on facilitation. The time course of the inhibition decline seen after TMS in individuals with subcortical stroke followed the gain in motor recovery.\(^3\)

### 3.3 Silent Period

Braune et al (1995)\(^2\) found that the SP interside differences increased according to the degree of motor impairment. In most of the patients examined, SPs were prolonged in the DH, but were reduced in a small minority (24\%). Despite this anomaly, the authors concluded that interside differences in SP, generally with prolongation of SP to the DH, is a sensitive indicator of damage to the central motor system caused by ischaemia.\(^2\)
Twenty-five patients with different degrees of stroke-induced impairment had TMS applied to the vertex during sustained muscle contraction; electromyographs were recorded from the ADM on both sides. In healthy individuals, there were no interside differences which were statistically relevant to duration of SP, although there was marked interindividually variation. In stroke patients, postexcitatory inhibition from the DH was significantly prolonged, with some instances of shortening when compared with the UH. The interside difference between SPs was significantly greater than in healthy individuals. When the ratios of SPs, both longer and shorter, were calculated, the group differences were even greater. The authors concluded that SP measurement provides a very sensitive neurophysiological parameter for motor system assessment.

The SPs of 49 hemiparetic stroke patients were investigated 7 and 90 days (D7 and D90) post-stroke. Patients who recovered well, as with healthy individuals, had stable SPs during voluntary isometric contraction. In patients with poor recovery, however, mean SP values decreased with increasing voluntary isometric contraction. The authors concluded that low SP values in the early stages of stroke are correlated with eventual spasticity.

Silent period changes were monitored in 50 acute hemispheric brain infarction patients. The SPs elicited were on the DH in 29 of the patients (58%). The mean SP duration was significantly greater on the damaged side, but there was no significant difference between the MEP amplitude ratio and MEP latencies on the left and right sides. In total, 86% of the patients had prolonged SPs, while only 4% had abnormalities in MEP amplitude ratio or latency. A subgroup of 14 patients with normal hand function had significantly prolonged mean SP duration. It was concluded that SP measurement can detect even subclinical disturbances to the motor system caused by ischaemic stroke.

Changes in SP caused by TMS were evaluated in 23 stroke patients with mild hemiparesis. The SPs for stroke patients’ hemiparetic side were significantly prolonged when compared with that for the normal side, while interside SP ratio was significantly greater than for healthy individuals.
SECTION 4 THERAPEUTIC TECHNIQUES

4.1 Transcranial Magnetic Stimulation and Brain Modulation

In stroke, cortical excitability is reduced in the affected parts of the motor cortex while the topographical representation of the affected muscles is suppressed. Meanwhile, increased excitability is seen in unaffected motor cortex areas, along with increased cortical motor output. It is possible to use TMS to modulate cortical excitation, thus improving motor function. An overview of current research follows, arranged according to year.

In 1999, Oliveri et al. discovered that patients with damage to their right hemisphere reacted positively to single pulse TMS over the left frontal cortex (intact hemisphere). The TMS sessions were given once a suitable interval had passed following completion of a bimanual discrimination task. These TMS sessions reduced the quantity of extinctions of tactile stimuli seen when the aforementioned stimuli were applied to the contralateral hemispace. This team also discovered, however, that TMS over the UH of patients with damaged left hemispheres had no significant effect on the recognition of stimuli applied to the contralateral hemispace.

Eleven healthy subjects underwent TMS of the frontal and parietal parts of each hemisphere during the cue-target interval between cutaneous electrical stimuli. Parietal stimulation of both hemispheres caused reduced detection sensitivity for near threshold stimuli in the forearm contralateral to the stimulated hemisphere. Parietal TMS did not influence ipsilateral tactile perception and frontal stimulation of either hemisphere did not cause changes in perception. The authors concluded that applying TMS to the parietal lobe in stroke patients could possibly aid in improving attentional deficiencies.

For 10 days, sham repetitive TMS (rTMS) or real rTMS was applied daily to the motor cortex of 26 acute ischaemic stroke patients. The patients were randomly assigned to the sham or real groups. Disability scores were improved in those patients receiving real rTMS, but no improvement was seen in the patients receiving sham rTMS.

Mansur et al. (2005) applied slow-frequency rTMS to the intact hemisphere of stroke patients within 12 months of their stroke to decrease interhemispheric inhibition of the DH and improve motor function. According to the authors, a significant decrease was seen in both simple and choice reaction times; patient performance on the Purdue Pegboard test with the affected hand also improved.

Four aphasia patients who were 5-11 years post-stroke were given slow, 1 Hz rTMS daily to the anterior of the right Broca’s homologue for 10 days. Picture naming skills improved significantly at 2 months post-rTMS, with 3 of the patients experiencing lasting benefit at 8 months. The authors concluded that rTMS could be of use in aphasia treatment.

Takeuchi et al. (2005) discovered that cortical stimulation of the contralesional M1 in stroke patients using rTMS (1Hz stimulation) reduced transcallosal inhibition (TCI) and improved the
motor function of the affected hand. The authors concluded that 1Hz rTMS improved the motor function through reducing TCI from the contralesional M1 to ipsilesional M1.

Also in 2005, Tsuji et al. gave motor point stimulation coupled with rTMS to nine patients left with hemiparesis following a stroke. All patients were right handed and the mean time from stroke was 80 days. The MEPs were measured in the affected FDI muscle immediately after and at 10, 20 and 30 minutes following stimulation. A significant increase in MEP amplitudes was seen immediately following pairing stimulation; amplitude levels recovered to baseline after 30 minutes. The authors concluded that corticomotor excitability was increased by paired stimulation and that this may be of potential therapeutic use during stroke rehabilitation.

A single stroke patient with severe motor impairment was given rTMS and placebo rTMS over the primary motor cortex of the UH. Motor function significantly improved following active rTMS but not during placebo rTMS. During an additional rTMS session, the patient both maintained and increased on the initial motor improvement. Patients with severe motor impairment are not, in general, treated with rTMS, but this study suggested that the technique might also be beneficial in these patients.

Di Lazzaro et al. (2006) proved once and for all that corticospinal activity was enhanced by non-invasive stimulation of a chronic stroke patient.

According to Kim et al. (2006), rTMS provides a non-invasive therapeutic stimulation technique that allows the effective modulation of cortical excitation in stroke patients. The authors stimulated the motor cortex, targeting the affected hemisphere using high-frequency, focal 10Hz rTMS in conjunction with motor practice intervention. Sham rTMS was used as a comparator. Combining the rTMS and motor practice therapeutic techniques led to increased movement accuracy and movement time than for sham rTMS combined with motor practice (P<0.05), suggesting that subject movement accuracy and speed were enhanced. Stimulation with rTMS also caused the mean peak amplitude of the MEPs produced to increase considerably when compared with sham rTMS (P<0.01), suggesting that using focal rTMS to modulate affected motor cortex causes the enhancement of corticomotor excitability associated with motor skill acquisition. No side effects were reported during this study. The authors concluded that high frequency rTMS is both a safe and an effective method of increasing cortical excitability and of enhancing the time taken for and the accuracy of motor performances during complex finger movements. They also highlighted that the plastic changes that had occurred in the motor cortex had taken place in chronic stroke patients even after the maximal time of potential motor recovery had been reached.

The long-term effects of low-frequency rTMS over the undamaged posterior parietal cortex on unilateral spatial neglect was explored in two chronic-phase stroke patients with left-sided unilateral spatial neglect from cerebral infarction. The patients were given 6 rTMS sessions over 2 weeks, with 900 stimuli given over the P5 at 95% MT, 0.9-Hz frequency per session. Test scores were remarkably improved, especially from 2-4 weeks post-rTMS. At 6 weeks post-rTMS, the test scores were still above the pre-rTMS levels. It was concluded that rTMS reduced neglect for at least 6 weeks.
It is known that suppressing activity in the contralesional motor cortex may be useful in promoting functional recovery following stroke. The depressant effects of low-frequency rTMS may be prolonged and increased if it is preceded by 6-Hz priming stimulation. Carey et al (2007) used this technique in 10 patients with ischaemic stroke to assess its safety. The priming sessions involved 10 minutes of 6-Hz rTMS over the contralesional hemisphere at 90% resting MT. This was delivered in 2 trains per minute where each train lasted 5 seconds and the interval between trains was 25 seconds. This priming session was followed by low-frequency rTMS, where an additional 10 minutes of 1-Hz rTMS at 90% resting MT was administered without interruption. The treatment, along with pre- and post-test assessments, took place on the first day; follow-up occurred on the next 5 weekdays. The treatment elicited no seizures and there was no lasting impairment of stroke measurement scores. Side effects seen included transient tiredness and occasional headaches, neck pain, reduced sleep, increased sleep, anxiety and nausea. It was concluded that the treatment was safe in the small cohort examined, but that further study in larger groups is necessary to confirm this.

Jayaram et al (2007) combined suprathreshold TMS with electrical stimulation in a technique known as paired associative stimulation (PAS). During the study, inhibitory PAS was applied to the contralesional motor cortex in patients with chronic stroke. The authors discovered that applying PAS to the contralesional lower limb motor system increased motor excitability in the paretic lower limb of chronic stroke patients when walking, suggesting that PAS could be a successful adjuvant therapy for stroke patients experiencing difficulty in walking. It was concluded that PAS may also be used to study recovery of the motor cortex responsible for lower limbs following stroke damage.

Lomarev et al (2007) discovered that rTMS rates of 20 and 25 Hz using above threshold stimulation had the potential to increase seizure risk in patients with chronic stroke.

The use of rTMS and voluntary muscle contraction as a means of improving muscle function, corticospinal transmission and purposeful movement in the early post-stroke period was investigated. Twenty-seven patients were assessed at a mean of 27 days following middle cerebral artery infarct using a protocol of 200 1Hz stimuli delivered at 120% MT to the DH in 5 blocks of 40 set 3 minutes apart. The MEPs increased in the rTMS + voluntary muscle contraction group by 14% for the biceps and 20% for the triceps. A decrease of 12% for the biceps and 6% for the triceps was seen in the placebo rTMS + placebo voluntary muscle contraction.

Six patients with chronic stroke and incomplete hand recovery were examined using three types of stimulation: excitatory theta burst stimulation over the stroke hemisphere (iTBS(SH)), inhibitory TBS over the intact hemisphere (cTBS(IH)), and placebo stimulation. Simple reaction times for the paretic hand decreased immediately post-iTBS(SH); compared to the placebo, these times remained significantly shorter throughout the testing period. Resting and background contraction MEP amplitudes also increased on the damaged side following iTBS(SH), as did input-output curves. Motor evoked potentials were evoked in the healthy hand by cTBS(IH), but there was no change in motor behaviour or electrophysiology of the paretic hands. No side effects were seen.
4.2 Transcranial Magnetic Stimulation and Constraint-Induced Therapy

Fregni et al (2006) studied the effect of 100% MT, 1-Hz, 1,200 stimuli rTMS delivered as a single, continuous train, 20 minutes in length and given consecutively for 5 days, on reaction time in the affected hand. Their results showed that a mean decrease of 70.94ms was seen for reaction time following each rTMS session. They also showed that the improvement seen in motor function was specific to the treatment given, increased over time and was long lasting, with effects lasting for up to two weeks following treatment completion. During the trial period, inhibitory low-frequency rTMS caused corticospinal excitability within the UH (stimulated) to decrease while it correspondingly increased in the DH (contralateral). Given over 5 days, rTMS decreased neural activity in the UH, suggesting that it could be a form of ‘central’ CIT. Since restricting use of an intact limb through CIT for 1-2 weeks can lead to a permanent change in the ability to use the affected limb, daily inhibition of the affected hemisphere via rTMS may well mimic the effects of a prolonged course of CIT and induce similar changes.

Despite the conclusions drawn by Fregni et al (2006), Malcolm et al (2007) found that rTMS had no effect as an adjunct to CIT. Any improvement seen in 19 patients, one or more years post-stroke, was attributed to treatment with CIT.
SECTION 5   ECONOMICS

5.1 Economic Effects of Stroke

Economically, stroke has a huge effect, with almost 5% of the medical costs of industrialised countries given to the disease. Although in real terms morbidity is relatively low, the long-term impairments left behind are hugely detrimental both in terms of hospital and other care sector costs. In the past, the greatest prevalence of stroke has been in the developed countries, but a change in this pattern may be expected as more and more countries adopt a more Westernized way of life. In 2002, stroke caused 5.5 million (approximately 10%) of all deaths worldwide; yet another 5 million worldwide were left permanently disabled. The UK Stroke Association believes that mortality from stroke will have almost doubled by 2020 as the proportion of elderly increases and because of current smoking patterns in the developing countries. An unseen cost in stroke is the effect it has on those caring informally for the survivors. These carers often have to change jobs or even careers, become the sole bread winner and, depending on the country they live in, deal with escalating medical costs for treatment.

5.2 Costs per Country

5.2.1 Canada

In Canada, stroke incidence is estimated as 40,000-50,000 strokes per annum. The effects of stroke are considerable, with 15 in every 100 individuals who suffer a stroke dying as a direct result of the disease. Of those who do survive, only 10 in every 100 will have a complete recovery, 25 in every 100 will be left with only minor impairment or disability, 40 in every 100 are left with moderate to severe impairment, while 10 in every 100 are left so severely affected by the stroke that they require long-term care.

In real terms, the costs to the Canadian economy are $2.7 billion a year, with an average of $27,500 being spent, per stroke, on acute care. In total, 3,000,000 days are spent by Canadian stroke sufferers in hospital per year, which again is a severe drain on the economy.

5.2.2 United Kingdom

In the UK, approximately 150,000 individuals suffer a stroke per annum. Over 67,000 (>45%) of these individuals will die as a direct result of suffering a stroke. It is estimated that over 300,000 people in the UK are living with the results of stroke. In England and Wales, the incidence of stroke is estimated at around 130,000 individuals. Approximately 10,000 of these will not have reached retirement age.

It is estimated that direct cost to the National Health Service is £2.8 billion; the cost to the economy as a whole is estimated as £1.8 billion. The cost of informal care to
stroke sufferers (i.e. care by non-specialists, e.g. family members) is estimated to be £2.4 billion. The costs of stroke care are expected to rise by 30% of the 1991 levels by 2010.

5.2.3 United States of America

In the USA, roughly 700,000 individuals will have a new or recurrent stroke; an average of 1 stroke every 45 seconds. Mortality is over 150,000 individuals per annum; in real terms 1 person dies every 3-4 minutes with 1 death occurring for every 16 strokes. More women die of stroke than men.

The expected expenditure for stroke-related medical costs and disability for 2007 alone is $62.7 billion.

5.2.4 China

During 1984-2004, the rate of ischaemic stroke occurrence in China rose by almost 9%, a growth attributed by researchers to rapid economic growth and development, and although no figures are given for expected expenditure, given China’s population, it is expected to be very high.

5.3 Cost of Caring for Stroke Survivors

The carer often has to take the brunt of the long-term effects a stroke has on the individual care for. A common complaint is that the carers are given no real help in caring for a stroke survivor despite being, in some cases, woefully unprepared and unsuitable for such a role. A study published in 2004 assessed whether providing training for the carer has an impact on the cost of care. It was discovered that health and social care costs for patients whose carers were trained were lower by approximately £4,043. Informal care costs were, however, similar between both groups.
SECTION 6  CONCLUSIONS

Stroke has serious consequences for the global economy and predictions are gloomy. With nearly 10% of all deaths worldwide being caused by stroke and with 5 million survivors being left permanently disabled in some way in 2002, the situation is of concern. According to the WHO, there is a 60% mortality or dependence rate even where access to new technologies and expert facilities is available, making it imperative that new treatments and technologies are discovered and exploited in the battle against stroke. Another main focus must be easing the burden on the carer, making rehabilitative methods high priority. The ultimate goal would, of course, be total rehabilitation of the patient, this allowing their return to work and a decent quality of life.

Transcranial magnetic stimulation has an important role to play in the fight against stroke and its consequences, whether as a prognostic technique, or as a rehabilitative method. Further research is needed to decide in which area TMS may be best utilised, but the research undertaken so far is very encouraging.

In short, the high incidence of death and permanent disability associated with stroke incidence, coupled with a very high treatment cost, makes it imperative that better stroke prevention and care is freely available and implemented, and TMS will play an important role in these improvements.
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