Plasticity after acute ischaemic stroke studied by transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is an established technique in which a painless pulse of fast rising magnetic field is used to induce an electric current intracranially, causing depolarisation of nerve membranes and the generation of action potentials. It produces early motor responses trans-synaptically via the pyramidal tract. There are other effects, which are subject to changes in the GABAergic and monoaminergic systems and in sodium and calcium channel properties, the first of these showing particular relevance to human plasticity. In addition to the familiar clinical studies of central motor conduction time, TMS is used for single motor unit studies, mapping of the motor cortex, the determination of motor threshold or cortical excitability, intracortical inhibition and facilitation studies (using a paired pulse protocol, to express interneuronal connectivity involving the motor cortex), stimulus-response recruitment curves, sensory studies (including the production of phosphenes), and for the targeted disruption of motor or cognitive task performance. Triple stimulation protocols can provide quantitative data on central conduction failure and mapping studies with TMS can be coregistered with structural and functional MRI or used for the study of functional connectivity across brain regions when combined with simultaneous PET.

A combination of these approaches have now converged on several themes, including the study of excitability changes and plasticity after stroke. Transcranial magnetic stimulation has started to provide support for at least two models of reactive motor changes, in which adaptive reorganisation seems to involve cortical areas that may or may not have been implicated originally in the function of the infarcted area (vicariation and substitution, respectively). These models have stood the test of time but now require thorough re-examination, in parallel with recent elegant work in the monkey. The seeds of these two processes are identified within the studies reviewed briefly here, from a combination of changes in excitability and in functional connectivity to TMS.

Clinical prognosis and outcome

In the course of acute ischaemic stroke, blood flow falls to a critical threshold producing a potentially reversible loss of electrophysiological activity. Irreversible damage can occur minutes later if flow continues to fall, when aerobic mitochondrial metabolism fails. This two stage process is associated with the establishment of multiple molecular, spatial, temporal, and cellular penumbras around the gross lesion in a shifting pattern. Within or beyond this, any spatial, temporal, and cellular penumbrae around the gross associated with the establishment of multiple molecular, mitochondrial metabolism fails. This two stage process is likely to express the net motor functional affects of these heterogeneous pathological and clinical events across the combined levels of organisation from cortex via brain stem, cord, and beyond.

Motor evoked potentials (MEPs) to TMS are often absent in the most severely affected patients, whereas in milder strokes they are usually of longer latency or smaller in amplitude, occurring at a raised stimulation threshold. Preserved MEPs in the early clinical stages correlate with a good functional recovery, although a difference in responses from affected and unaffected hands can persist. In the remainder, upper limb MEPs often pre-empt the return of residual function and are correlated with subsequent muscle strength. The more difficult prediction of outcome in the intermediate degrees of severity can be augmented by the combination of TMS with somatosensory evoked potentials (SEPs). The degree of any subsequent clinical impairments can correlate less well with MEP abnormalities, but sometimes better than with the size of lesion on CT.

In lacunar infarcts, electrical (rather than magnetic) transcranial stimulation can produce abnormalities that correlate with clinical pyramidal signs in more than 50% of those patients with relatively minor ischaemia, with prolonged central conduction times and increases in stimulation threshold, correlating with the level of clinical weakness and with the presence of brisk tendon reflexes, respectively. Although there is some evidence for ipsilateral reorganisation (mediated possibly by the corticoreticulospinal tract), ipsilateral MEPs seem only rarely to be related to distal limb function after cortical strokes. In those cases with apparent spontaneous recanalisation indicated by transcranial Doppler ultrasound (TCD), central motor conduction times to TMS improve significantly more than in those patients without appropriate TCD changes.

In terms of specific physical signs and their correlates, a silent period naturally follows the MEP, an acute shortening of which has been associated with poor functional recovery and with the appearance of spasticity. After the development of spasticity, however, a combination of voluntary precontraction and vibration of the target muscle can produce a facilitated response to TMS, with silent periods sometimes appearing in the absence of an MEP. Finally, in longitudinal studies, clinical improvements appearing several months after an acute stroke have been coupled with MEP and threshold improvements that are particularly noticeable in the first 80 days, which suggests a window for the most active plastic changes during functional motor reorganisation.
muscle can also be determined. It should be noted that maps usually have an operational definition, therefore, and are method dependent as in most imaging techniques. Furthermore, measurements are usually subject to constants such as age and depth of cortex, and to variables including motor inhibition with stroke may correlate.

Nevertheless, these maps are reliable and can be coregistered digitally with MRI for cross sectional or longitudinal studies. In healthy subjects they project closely to cortical areas activated by hand movements during PET or functional MRI.

Some TMS mapping studies support the presumed role of functional reorganisation via the corticospinal projection from the lesional hemisphere in the recovery of motor function after stroke. In addition, patients with subcortical lesions that spare the motor cortex are shown with TMS to have the potential for cortical reorganisation which can be greater than that after lesions to the cortex itself. In such patients with lacunar infarcts, map shifts have been found in patients with lesions including the posterior limb of the internal capsule (which conveys the corticospinal tract) but not in patients with a lesion in the anterior limb or the genu (although fibres from non-primary motor areas do traverse that part of the capsule). Serial studies confirm the stability of TMS maps over the non-lesional hemisphere, which can be quite prominent in patients who have made notable clinical recoveries from subcortical strokes.

In one particular serial study of patients after their first ischaemic stroke in MCA territory, a high motor threshold for small hand muscles was found on day 1, with a subsequent gradual reduction which correlated with clinical improvement. Thresholds on the non-lesional side were significantly reduced in the first week and map volumes (area multiplied by amplitude) were larger. The presence of a preserved MEP on the lesional side on the first day was also found to be positively correlated with motor recovery (with an inverse correlation between the volume of the brain CT lesion and hand motor recovery, as well as with Barthel scores). Map centre of gravity was slightly displaced frontally on the lesional side between the 2nd and 4th week in this study, with a similar milder change occurring on the non-lesional side. The non-lesional hemisphere in another group has also shown a reduction in motor inhibition on TMS in chronic stroke as well as the presence of plasticity in the lesioned hemisphere.

These and other studies imply that clinical recovery is related to a plasticity of corticospinal excitability combined with changes in anatomical reorganisation or functional connectivity, including the lesional and non-lesional hemispheres.

Proximal and midline musculature can be of particular clinical importance after stroke. Transcranial magnetic stimulation studies of normal swallowing show a bilateral corticobulbar projection, with asymmetric distributions between the two hemispheres. Recovery from dysphagia after unilateral stroke is associated with an increase in the excitability of remaining projections from the non-lesional hemisphere. By contrast, the map area for a small hand muscle increases, mostly on the lesional side. Normal shoulder muscles also show an asymmetric bilateral projection, with ipsilateral pathways being slower than the contralateral one and with one or other hemisphere usually being dominant. Such findings highlight the possible role of ipsilateral projections after stroke and may correlate with the relative preservation of proximal upper limb muscle strength. The recovery of lingual function also seems to be dependent in part on function of the non-lesional hemisphere.

Transcranial magnetic stimulation and restorative neurology

Transcranial magnetic stimulation has been used to monitor therapy, and several groups are beginning to experiment with its potential therapeutic applications in improving the rate of recovery. In a TMS study of small hand muscles, patients at 4 to 8 weeks after their infarction were studied before a single session of physiotherapy, and then at 1 hour and at 1 day afterwards. Before training, map area on the lesional side was significantly smaller than on the non-lesional side. After physiotherapy, map area from the affected side was enlarged in association with an improvement of motor function in most patients. One day later, these effects were partially reversed, although motor threshold remained significantly increased in the lesional hemisphere before and afterwards. The technique can therefore show a use dependent enlargement of map area. Furthermore, patients with chronic stroke studied before and after 2 weeks of constraint induced movement therapy (where patients are unable to depend on their constrained good arm) have shown an increase in TMS excitability of the lesional hemisphere. The centre of representation also shifted in this study, implying recruitment of additional cortical regions adjacent to the original representation. These changes were associated again with an improvement in clinical motor function.

To conclude, TMS has provided reproducible physiological correlates for acute and chronic clinical and imaging changes that underlie some of the pathophysiology, prognosis, topography, and potential for rehabilitation after ischaemic stroke, of cortical and subcortical territories. These data seem to support the appearance of motor plasticity via a variable combination of variation and substitution, in association with changes in excitability and functional connectivity involving the lesional and non-lesional hemispheres.

To invoke the plasticity of normal learning in this context, TMS experiments have confirmed recently that the human motor cortex itself has a role in normal rapid motor learning of changes in force and acceleration, in a manner that can be specific to the task and to the effector muscle. One future challenge will be to exploit such features and structures common to developmental and reparative plasticity, therefore, in a way that can close the gap between them in providing a basis for targeted plasticity via a variable combination of variation and substitution from TMS can probably be expected in close combination with animal models of stroke, human genetics, functional imaging, and with pharmacology aimed again at closing two further gaps; those between gene induction and measurable human physiology on the one hand and between all these complex basic principles and therapy, on the other.

S J BONFACE

Department of Clinical Neurophysiology and Welfson Brain Imaging Centre, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK

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Neuropsychiatric phenomena in Alzheimer’s disease

The three expressions of the clinical syndrome of dementia have been well documented: cognitive deficits—amnesia, aphasia, apraxia, and agnosia; neuropsychiatric features—a heterogeneous array of psychiatric symptoms and behavioural disturbances such as depression, delusions, hallucinations, misidentifications, aggression, agitation, wandering, collectively described as neuropsychiatric features; and problems with activities of daily living. The history of interest in the neuropsychiatry of dementia is relatively short by comparison with research into cognitive dysfunction. Psychiatric symptomatology was only first described in detail in the 1980s and 1990s and has only recently been the subject of standardised and reliable methods of assessment (for example, the neuropsychiatric inventory).

In the paper by Holmes et al (this issue pp 777–779), the field takes a significant step forward in identifying some of the biological determinants of the expression of neuropsychiatric symptoms in Alzheimer’s disease, the commonest cause of dementia.

Some aetiological factors have been implicated in the genesis of neuropsychiatric features. In Alzheimer’s disease, associations have been described between the degree of neuronal loss and the histological changes of Alzheimer’s disease with the presence of behaviours such as aggression and hypermetamorphosis. Changes in the amineergic brain stem nuclei are more pronounced in patients with Alzheimer’s disease who have had depression. Increased sophistication of the measurement of neuropsychiatric features has emphasised that assessments of their phenomenology and occurrence are essentially drawn from the reports of caregivers. It is known that the environment in which a patient finds him or herself is a potent predictor of the presence of some behaviours (such as agitation) and often the interaction between a patient and carer (whether this be a paid or informal carer) can promote a reaction which can easily be interpreted and recorded as indicating the presence of a psychiatric symptom. Sensory deprivation such as poor vision and poor hearing can promote the presence of visual hallucinations and paranoid beliefs respectively.

The availability and ease of measurement of genetic markers in Alzheimer’s disease has led to investigations examining the association between these biological markers and psychiatric symptoms.

The importance of neuropsychiatric features in dementia are that they are very distressing to patients and carers, they are amenable to both environmental and pharmacological interventions, they may help in the differential diagnosis of the causes of dementia, and they may shed light on biological substrates of phenomenology in so called functional psychiatric disorders. They underscore the important role of the psychiatrist in the assessment and management of the dementias and, increasingly, in the understanding of the biological substrates of phenomenology.

A BURNS
School of Psychiatry and Behavioural Sciences, Department of Psychiatry, Wollongong Hospital, West Didsbury, Manchester M20 8LR, UK

Correspondence to: Professor A Burns
a.burns@fs1.with.man.ac.uk