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 subsequent reactive plasticity that may occur subsequently is probably dependent on gene induction. Analysis of motor function by TMS, before or after any intervention, 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.

Topographic mapping
There are methods for mapping with TMS. Figure of eight coils provide a moderately focal stimulus and can be used to determine the number of excitable scalp positions for a given muscle, the location of optimal positions for stimulation (becoming known as top one third techniques), the centre of gravity (which is an amplitude weighted representative position of a motor map), and the stimulus/response relations acquired at one or more scalp sites. The optimal direction of currents necessary to activate a
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 vicariation 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 to reparative plasticity, therefore, in a way that can close the gap between them in providing a basis for targeted efficacy and safety of restorative therapy. Future developments 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.

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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;5 or non-cognitive features;6 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 increased sophistication of the measurement of neuropsychiatric features.7,8 A common substrate of neuropsychiatric symptoms in Alzheimer’s disease is neuronal loss and the histological changes of the neurofibrillary tangle and neurodegeneration.9

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.10

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.

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