Primer

Transcranial magnetic stimulation

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As any schoolboy with a toolkit or a broken toy soon appreciates, to find out how a machine works you need to take it apart, and to put it back together again, you need to know how it works. The next lesson is that, no matter how hard you try, you always end up with a handful of leftover nuts and bolts. These remaining components can be informative: will your machine still work without them? The same logic applies to one approach to understanding human brain function: by investigating the effects of lesions in animals and accidental brain damage in humans we can ask which parts are necessary for specific functions. Over the past twenty years, it has become possible to interfere with human brain functions safely and reversibly, and to control when and where the interference is induced. The technique, known as transcranial magnetic stimulation (TMS), has become a mainstay of cognitive neuroscience.

What is TMS?

TMS is based on the principle of electromagnetic induction. Michael Faraday showed that when an electrical current is passed through a wire, it generates a time-varying magnetic field. If a second wire is placed nearby, the magnetic field induces electrical current flow in that second wire. In TMS, the 'first wire' is the stimulating coil and the 'second wire' is a targeted region of the brain.

The most common coil in use in TMS is a figure-of-eight shape in which electrical current flows in opposite directions around each of the windings, converging at the centre-point where the currents summate. This allows one to target focal regions of cortical tissue. The coil is placed on the scalp, and the resulting magnetic field passes through the skull and induces an electrical field in the underlying cortex. The effect is to stimulate neuronal activity and change the excitation and organisation of neuronal firing in the stimulated region.

Since Anthony Barker and colleagues first demonstrated TMS in 1985 it has been used widely to stimulate both peripheral nerves and brain tissue in studies encompassing motor conduction in human development, motor control, movement disorders, swallowing, vision, attention, memory, speech and language, epilepsy, depression, stroke, pain and plasticity. It has proved to be a versatile technique and is now also being used in combination with electroencephalography (EEG), functional magnetic resonance imaging (fMRI) and single unit recording.

Pulses of TMS can be applied at varying intensities, and in single pulses or in repetitive trains (rTMS) of low or high frequency. The choice of stimulation parameters determines whether the effects of stimulation are excitatory or inhibitory. For example, two single pulses separated by less than 5 milliseconds can produce intracortical inhibition, while two single pulses separated by a gap greater than 10 and less then 30 milliseconds can produce intracortical facilitation. Repetitive TMS at a frequency of 1 Hz has the effect of depressing cortical excitability for a period of time after the train of pulses has finished, whereas repetitive stimulation at 10 Hz or more may increase excitability. Theta burst stimulation, applying trains of 50 Hz stimulation in bursts every 200 milliseconds, has the effect of depressing cortical activity for a period following stimulation. Theta has been used in few studies but its effects are clearly more reliable than those of 1 Hz.

Although stimulation effects are maximal in the cortical region directly underneath the coil, TMS also has secondary effects on connected areas of cortex, and these are useful in both basic and applied studies. If one stimulates, say, the left motor cortex, there are three likely effects of stimulation: a change in activity in the targeted region; a change in activity in immediately surrounding areas of cortex; and a change in the activity of cortical areas directly connected with the stimulated region. These are important considerations in preventing naive interpretations of the effects of TMS, and also in allowing for studies of cortico-cortical interactions (see below).

There is sometimes a misconception that TMS is a spatially crude technique, but the effective resolution may be in the order of a few millimetres and very good inferences can be made about the physiological effectiveness of the stimulation area. TMS over primary motor cortex evokes muscle twitches from the fingers, hand, arm, face, trunk and leg in a manner that matches the organisation of the motor 'homunculus'. Positioning the coil on the scalp at locations spaced between 0.5 and 1 cm apart is sufficient selectively to activate these different muscles.

A similar effective spatial resolution has been demonstrated in primary visual cortex. Depending on the intensity and experimental conditions, TMS over occipital (visual) cortex causes people to experience either a spot of light (a phosphene) or a blind spot (a scotoma) in their visual field. The location of the phosphene or scotoma corresponds with the coil position over the visual cortex. With coil positions 0.5–1 cm apart, the region of the visual field in which the phosphene or scotoma is induced can be controlled with an accuracy as precise as 1° of visual angle (estimates of the cortical distance representing the central 2° of visual angle of between 20 and 30 mm).

Outside primary sensory and motor cortices, spatial resolution must be inferred from diminishing effects of TMS on cognitive tasks. The induced current dissipates rapidly with distance from the centre of the TMS coil. Thus, spatial resolution can be estimated effectively by measuring how a stimulation-induced behavioural effect — an increase in reaction time or the frequency of errors, for example — dissipates as the coil is moved gradually away from a targeted cortical site. Studies that have combined TMS with imaging methods have shown good correspondence between the spatial extent of a functional region defined in such a way by TMS and that defined by other measurement techniques.

TMS as an interference technique

The effect of TMS is to induce activity changes, excitatory or inhibitory, that are effectively random with respect to the organised signals required to perform a task. This is an important yet often misunderstood point. Stimulating the motor cortex will make a subject's hand twitch and will make it harder for him or her to point accurately at or grasp an object. It will not cause the subject to produce an organised action. Stimulating the visual cortex will cause subjects to see a blur or a flash of light, or will make it harder for them to detect or identify a visual object. It will not make them see a country scene or see the words on a page more clearly. In this sense the application of TMS introduces noise into the system being stimulated, and it can therefore be employed as a lesion technique with many advantages over lesion studies in neuropsychological patients and non-human animals. This concept of noise is also important in understanding reports of perceptual or cognitive enhancements induced by TMS.

A classic series of experiments on occipital cortex by Vahe Amassian exemplifies the use of TMS to induce what have come to be called 'virtual lesions'. Amassian showed that TMS applied after the onset of a visual stimulus — such as a three-letter (trigram) combination like 'TGN' — impaired subjects' ability to identify the letters. When subjects were shown two trigrams in succession, for example 'TGN' followed by 'XDU', the second trigram masked the first, and they were unable to identify the TGN stimulus accurately. When TMS was applied approximately 100 milliseconds after the second trigram, the induced neural noise weakened the representation of XDU and subjects were again able to identify the TGN stimulus.

This experiment illustrates two of the most valuable aspects of TMS as a lesion technique that make it an advance on traditional neuropsychological or animal studies: a temporal resolution in the millisecond range, and the ability to interfere selectively with competing representations, in this case that of the two trigrams. In the second experiment one might be tempted to conclude that TMS has improved vision, but it did so only by selectively interfering with a competing visual process. This logic of disinhibiting one function by suppressing another has been harnessed effectively in studies of plasticity.

TMS in plasticity and rehabilitation

TMS of sufficient intensity over the motor cortex induces muscle activity, measured as motor evoked potentials (MEPs), in the contralateral hand, because in a normal motor system each cerebral hemisphere controls movements of the contralateral effectors. This simple fact has allowed several groups to study short term remapping of the motor system, to assess the role of undamaged areas of motor cortex in recovery of function, and to explore the use of TMS for neurorehabilitation. John Rothwell and colleagues applied low frequency repetitive TMS to the motor cortex of one hemisphere in neurologically intact subjects, and used fMRI to observe TMS-induced changes in brain activity while subjects performed a finger movement task. They observed increased activity in the premotor cortex of the unstimulated hemisphere, and a changed pattern of interaction between the stimulated cortex and other motor regions, suggesting that the motor system is capable of functional remapping in response to interference from TMS.

In a related study, Heidi Johansen-Berg and colleagues demonstrated the potential importance of remapping in a group of patients who had suffered a left hemisphere stroke and consequent impairment in moving their right hand. First, the authors showed that stroke patients, compared to healthy controls, exhibited increased activity in motor areas of the undamaged hemisphere when performing finger movements with the stroke-affected hand. They then demonstrated the functional significance of this newly emergent activity by applying TMS while subjects performed the finger movement task with the stroke-affected hand: TMS caused significant reaction time delays in patients, but not in controls. This suggests that it may be possible to incorporate TMS into rehabilitation programmes — to change the relative excitability of and interactions between the two cerebral hemispheres.

Massimiliano Oliveri and colleagues applied this strategy to patients suffering from visuospatial neglect, a form of attentional bias where the subjects appear to be unaware of events in one half of their visual field. They applied transient repetitive TMS to the parietal cortex of the undamaged hemisphere while patients carried out a line bisection task (a common measure of attentional bias). They found that TMS transiently decreased the magnitude of neglect. This kind of work demonstrates the potential of applying TMS to neurorehabilitation.

It is appropriate to mention a methodological relative of TMS at this point. Transcranial direct current stimulation (TDCS) changes cortical excitability by the application of constant, weak electrical current to the scalp.

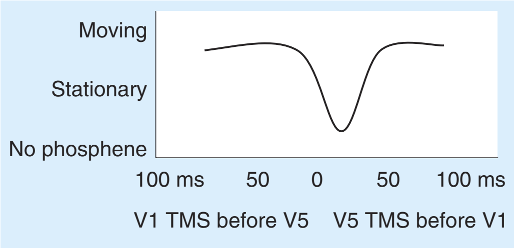

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Figure 1. An example of using the temporal resolution of magnetic stimulation to examine cortical connectivity.

This approach is based on the differential effects of high and low intensity stimulation and double coil stimulation. TMS was delivered over MT/V5 to induce the perception of movement and either preceding or following this pulse a single pulse of subthreshold TMS was applied over V1. The results show that the perception of movement was degraded or abolished when V1 stimulation post-dated V5 stimulation by approximately 15–40 milliseconds. (After Pascual-Leone and Walsh, 2001.)

It has several advantages: it can selectively excite or inhibit cortex depending on the polarity of the current; the changes in excitability can last for hours; it is especially useful in combination with pharmacological manipulations; and because it does not create acoustic noise or muscle twitch artefacts and is portable, it can be used with ease in patients. Walter Paulus' group in Goettingen have developed the use of the technique in as many areas as TMS is used, with impressive results. Following the findings of Johansen-Berg and colleagues, Leonardo Cohen's group applied TDCS to patients who had suffered a stroke and hemiparesis. All patients showed an improvement on measures of hand function and this improvement was correlated with increased motor cortex excitability in the damaged hemisphere. These are small beginnings for transcranial stimulation in plasticity and rehabilitation, but the potential is clear.

Studies of connectivity

A series of studies have exploited TMS-evoked phosphenes and the temporal resolution of TMS to explore back-projections from visual area V5 (MT) to V1 that may mediate awareness of motion. While phosphenes elicited by V1 TMS are stationary, those evoked from V5 are often moving. A TMS coil can be positioned over each area until the phosphenes evoked from either site overlap in space. The intensity of stimulation (threshold) required to produce a phosphene is then measured and a single sub-threshold or supra-threshold TMS pulse is applied over each site at various inter-pulse intervals. By varying the temporal interval and stimulation intensity, subjects' visual perceptions can be modified. When a supra-threshold TMS pulse over V5 is followed by a sub-threshold pulse over V1, subjects either fail to perceive phosphenes, or when they do they are no longer moving, but stationary (Figure 1). Conversely, a sub-threshold TMS pulse over V5 followed by a supra-threshold pulse over V1 causes subjects to perceive moving phosphenes of a size and shape that have a mixture of the properties of V1 and V5 phosphenes. These effects are only obtained when the second TMS pulse over V1 is delivered between 10 and 50 milliseconds after the first pulse over V5.

These results have also been extended to real moving stimuli, and critical periods for both feedback and feedforward processing have been identified. In combination, this set of studies argues that the perception of visual motion requires fast back-projections from V5 to V1, and that it is the level of activity in V1 that determines whether motion signals in V5 reach awareness. In the context of TMS as a technique they are a good example of how temporal resolution, knowledge of anatomical connections, and the use of TMS to both initiate and disrupt processing can be used to explore human cortical processes.

Combining TMS and other techniques

TMS is now routinely combined with other techniques, most commonly with anatomical MRI scans to coregister the position of the TMS coil on the scalp with the underlying cortical target site in individual subjects. It is also becoming increasingly common to use an fMRI precursor study to determine the sites of stimulation for a TMS study. Tomas Paus and Peter Fox were among the first to combine TMS with positron emission tomography, and their findings were important in showing that TMS applied over one brain region, such as the frontal eye fields or the motor cortex, can have secondary effects in anatomically connected areas. Similar findings emerged from the combination of TMS with EEG.

More recently, TMS has been combined with fMRI and EEG to investigate the functioning of these resting-state connections when they are recruited in the service of a cognitive task. Many of the technical problems of combining TMS with fMRI have been addressed, and the combination of techniques has demonstrated the importance of reafferent feedback from evoked movements to the motor cortex and remote effects of frontal eye fields on visual cortex. The main strength of TMS in behavioural studies is to parse behaviour in time, but a limitation of combined TMS and fMRI lies in the poor temporal resolution of fMRI. The combination of TMS with EEG, however, can enhance our temporal partition of behaviour and has already successfully revealed interactions between the frontal eye fields and visual cortex and between parietal cortex and visual cortex. Paul Taylor and colleagues applied magnetic stimulation over the frontal eye fields while subjects prepared to make a spatial response in a visual detection task. TMS modulated the electrophysiological signals measured from visual cortex both during the task preparation period, and in response to the presentation of a visual stimulus. Rich opportunities exist for further exploration of correspondences between behaviour, TMS and other physiological measures.

Little is known at the single-neuron level about the mechanisms mediating TMS effects. One recent study by Klaus Funke and colleagues reported that a single high-intensity TMS pulse applied to V1 neurons produced a temporal sequence of initial suppression of neuronal excitability, lasting about 100–200 milliseconds, followed by a period of rebound excitation. Understanding how such long suppression effects may cause interactions between TMS pulses delivered in trains will be an important step in clarifying the effects of repetitive-pulse TMS.

A final area of technical combination is that of using TMS in pharmacological studies. Following a demonstration that rTMS of motor cortex induces the release of dopamine in the putamen, Strafella and colleagues delivered rTMS to the motor cortex of subjects in the early stages of Parkinson's Disease (PD) and measured subsequent changes in dopamine concentration. In the patients' symptomatic hemisphere, the TMS-induced dopamine release was less than in the asymptomatic hemisphere but the area over which it was released was greater, suggesting a loss of specificity in corticostriatal communication in early PD.

Conclusions

In this Primer we have been able to give only a snapshot of the basic features and the applications of TMS. Some fundamentals of the use of TMS are falling into place as we learn more about the effects of different combinations of stimulus intensity, frequency, task and behavioural state. We have not had space to cover some important areas, such as studies of depression, language, eye movements and basic motor physiology, but the technique is now used in almost every area of cognitive neuroscience. Areas in which we can expect the next major advances in the use of TMS (and TDCS) include: the combination of TMS with other techniques to investigate causal interactions between cortical areas; the development of new paradigms to change selectively the baseline state of cortical excitation prior to further magnetic stimulation; and the incorporation of TMS into neuro-rehabilitation programmes.

Further reading

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Asymmetric tail-wagging responses by dogs to different emotive stimuli

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Research on behavioural asymmetries associated with specialisation of the left and right side of the brain has focused on asymmetric use of paired organs, such as forelimbs [1]. However, control of medial organs such as the tail would also be expected to involve hemispheric collaboration and, sometimes, competition. Here we report some unexpected and striking asymmetries in the control of tail movements by dogs: differential amplitudes of tail wagging to the left or to the right side associated with the type of visual stimulus the animals were looking at.

Thirty dogs, 15 intact males, 15 intact non-oestrus females, of mixed breed, with an age range of 1–6 years were tested. All were family pets whose owners had consented to participate in the experiment during periodic obedience and agility training in a behavioural dog school associated with the Faculty of Veterinary Medicine of Bari University, Italy.

The dogs were tested in a large rectangular wooden box (250 cm x 400 cm x 200 cm) uniformly covered inside with black plastic that prevented dogs from seeing outside. Illumination in the box was provided by four light bulbs (60 W) symmetrically located around the walls. The testing box had a rectangular opening (120 cm x 60 cm; 10 cm above the floor level) on the centre of one of its shorter side to permit the presentation of the stimuli. An opaque plastic panel, same size as the rectangular opening,