

Probing the mind with magnetism

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Transcranial magnetic stimulation is a technique that can be used to interfere reversibly with cortical processing. It creates a 'virtual lesion', which is relatively focal in space and time and can therefore be used to address questions beyond the scope of other techniques. In this article we select a few recent experiments that highlight the added value that TMS brings to some of the core areas of cognitive neuroscience: imagery, crossmodal processing, language, plasticity, awareness and memory.

According to the wizard Gandalf in *Lord of the Rings*, 'He who breaks a thing to find out how it works strays from the path of wisdom'. This is all very well for wizards to claim but cognitive neuroscientists, without the aid of magic spells, often rely on precisely this approach in order to understand brain function. Transcranial magnetic stimulation (TMS) is part of a long and successful line of techniques (including neuropsychology and animal lesion studies) that can be used to reverse-engineer the brain¹⁻³. It requires a magnetic stimulator, which consists of a capacitor and a stimulating coil (Fig. 1). An electric current, of up to 8 kA, is discharged from the capacitor into the coil, producing a magnetic pulse of up to 2T. If the coil is held against the subject's scalp, the rapidly changing magnetic field results in a localized electric field in the surface of the cortex. The resulting neural activity constitutes a kind of 'neural noise', superimposed upon the existing organized electrical activity, which temporarily disrupts functioning of underlying cortical tissue. This can result in the subject showing a reduced ability to perform a task of interest, in the same way that patients with circumscribed lesions might present with specific deficits. The 'virtual' lesions that TMS creates differ from the lesions seen in neuropsychological patients in two important ways: they are transient and they are reversible. These factors bring a new level of functional resolution to

the process of inferring whether a cortical area is necessary for the performance of a given function (see Fig. 2).

Capturing the imagination

As a virtual lesion technique, TMS has the power to demonstrate the functional necessity of a particular cortical region in neurologically intact individuals in a way that no other technique currently can. One field in which this feature of TMS has been exploited is that of visual imagery. Although topographically organized regions of visual cortex are activated during visual mental imagery⁴, it remains uncertain whether these cortical activations are merely correlates of the task. Kosslyn and colleagues⁵ recently used identical task conditions in a PET study and a TMS study. With their eyes shut, subjects visualized and compared properties of previously presented sets of stripes. The PET results showed activation of striate cortex.

The application of TMS over medial occipital cortex while subjects performed the same task increased reaction times (Fig. 3). The effect of TMS on reaction times was greater during visualization than when TMS was applied while the subjects performed the task without visualization. In this study, the activations seen during the PET scanning provided a hypothesis concerning the role of occipital cortex in mental imagery tasks, which could then be tested using TMS. But TMS has also been used concurrently with brain



Figure 1. The magnetic stimulator

A photograph of a commercially available magnetic stimulator, consisting of a capacitor and stimulating coil ('figure of eight'). An electric current of up to 8 kA is discharged from the capacitor into the stimulating coil, producing a magnetic pulse of up to 2T. The coil is placed over a region of scalp. The application of a magnetic pulse results in a localized electric field, which transiently disrupts functioning of underlying cortical tissue.



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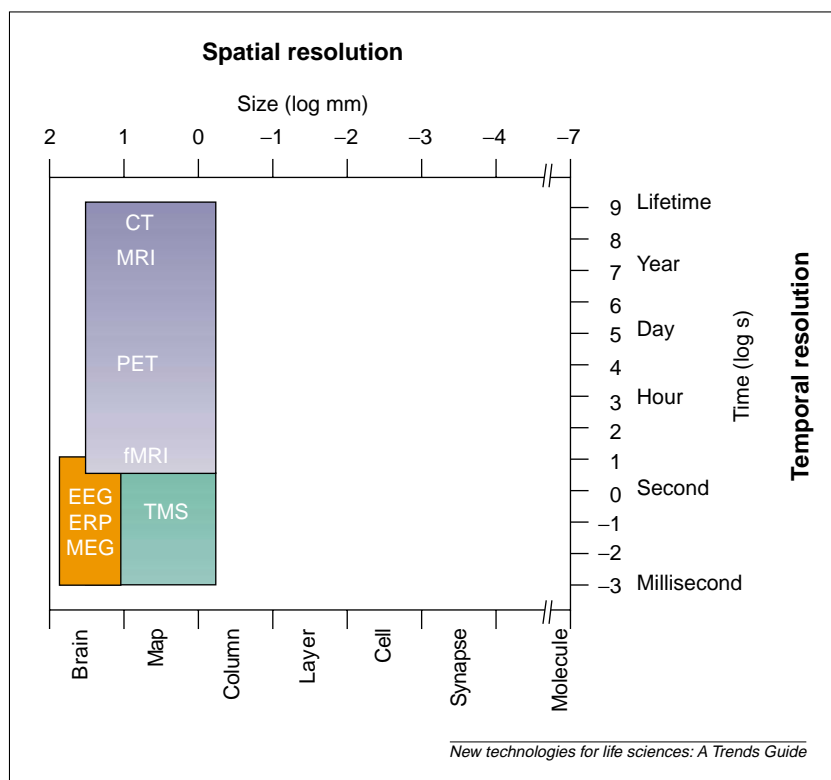


Figure 2. Spatial and temporal resolution of several methods commonly used in cognitive neuroscience

Temporal resolution, on the vertical axis, refers to the time scale over which the measure is obtained. Spatial resolution, on the horizontal axis, refers to the localizational specificity of the technique. Transcranial magnetic stimulation (TMS) has better temporal resolution and equivalent spatial resolution to techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

Abbreviations:
CT, computerized tomography;
EEG, electroencephalography;
ERP, event-related potentials;
MEG, magnetoencephalography.

imaging techniques^{6–10}, permitting visualization of the cortical effects of stimulation. This dual-technique approach will allow us to establish the extent of the spatial spread of stimulation, the effect of different stimulation parameters (rates and intensities) on regional cerebral bloodflow and the effect of stimulation on areas remote from the target site.

The touchy-feely side of vision

Much of the time, the hypotheses we seek to test are shaped by existing knowledge we have concerning brain function, such that hypotheses become increasingly more refined until we have a detailed theory of how the brain performs a given task. A potential problem of this approach is that it might prevent us from discovering important, counterintuitive, findings. A recent experiment illustrates how TMS has been used to step outside existing preconceptions to ask a somewhat daring question: is visual cortex also involved in non-visual perception?

Visual cortex has been shown to be active during non-visual perception in people who are blind^{11,12}, a finding which has been explained on the basis of non-visual neurons expanding into a deafferented cortical area. This seems a plausible explanation, but there are others. Is it possible, for instance, that visual cortex has a role to play in non-visual perception even in normally sighted individuals? Could the apparent 'hijacking' of visual cortex for non-visual functions in blind people merely represent an extreme case of what occurs in the normal brain?

In a recent PET/TMS study¹³, subjects who performed a task that required the discrimination of the orientation of a tactile grating on a fingerpad, reported using visual imagery. Activation of extrastriate visual cortex during the task was also seen. The crucial question was whether the visual imagery was being used to facilitate the tactile discrimination or was merely epiphenomenal. To address this question, TMS was delivered over the visual cortex of normally sighted subjects, and was found to significantly impair their performance on a task requiring tactile discrimination of grating orientation but not on a task requiring tactile discrimination of grating texture. This led the authors to make the tantalizing suggestion that visual processing is necessary for some, but not all, aspects of normal tactile perception.

In addition to illustrating how TMS can be used to challenge existing preconceptions regarding brain function, this study shows how TMS can bypass some of the limitations of classical neuropsychology. Deficits in tactile recognition of objects are rarely reported following damage to the visual cortex. This is probably because, immediately following the lesion, visual deficits are likely to overshadow the tactile deficits whereas, later, the brain will have had time to reorganize, possibly co-opting areas that would not normally be involved in performing the tactile discrimination task. With TMS, the transient nature of the 'virtual lesion' precludes the occurrence of functional reorganization so that the pure effect of the lesion can be seen. Conversely, in cases of tactile agnosia, the diffuse nature of the clinical lesions have prevented us from learning to what extent the deficit can be explained on the basis of damage to occipital cortex. TMS can help here by targeting single cortical areas, with surrounding areas serving as control sites. The virtual lesion thus produced is more circumscribed than normally occurs in real neuropsychological patients.

Lost for words

The use of TMS in the study of speech and language function has been relatively slow to gather momentum. A major reason for this is that the neural systems underlying language are highly complex and distributed in both hemispheres. Far from the once-held dichotomy, whereby language input and output were ascribed to Wernicke's and Broca's area respectively, functional imaging experiments have ascribed linguistic functions to a number of additional cortical areas, suggesting that language is represented in a highly redundant fashion in the brain. Disruption by TMS would, therefore, be much harder to achieve.

TMS studies of language fall into two domains, those looking at aspects of linguistic processing lying upstream of speech output and those looking at speech output itself. TMS has been shown to affect naming^{14–18} but, taken together, these studies do not provide a consensus regarding which sites are most vulnerable to disruption. A clearer picture emerges when we turn to the use of

TMS to produce speech arrest – possibly the most powerful example of TMS in its ‘virtual lesion’ mode. The interesting question here is whether the speech arrest results from interference at a cognitive or merely motor output level^{19,20}. A recent experiment in which recording electrodes were attached to the facial muscles suggests that speech arrest can be achieved by interference at either the cognitive or the motoric level depending on where the coil is placed (unpublished data). TMS applied over the Rolandic cortex of either hemisphere produced speech interference that was associated with activity of the facial muscles, whilst stimulation at a more anterior site of the left hemisphere alone produced speech disruption that was dissociated from such activity. Perhaps the latter site, over which TMS can produce a non-motoric type of speech arrest, would be a good site over which to start using subthreshold stimulation to test cognitive theories of linguistic function.

Malleable minds

The effect of learning on the brain’s functional architecture can be seen by looking at the cortical reorganization that occurs in stroke patients, amputees and the blind. From such individuals we know that when an area of the brain is deprived of its normal sensory inputs, neighbouring regions encroach into the deafferented area. Functional imaging techniques permit visualization of the cortical reorganization that occurs in response to skill learning in normal brains. TMS takes us a significant step further, by isolating functionally relevant cortical changes. Pascual-Leone and colleagues²¹ used TMS in the context of a motor-learning task to track learning-related changes occurring at a relatively low level in the processing hierarchy; specifically, in motor cortex. Subjects learned a one-handed, five-finger exercise on the piano keyboard, which they practised for two hours a day, for five consecutive days. By using TMS over the motor cortex to map the representation of the hand area, it was shown that, by day five, when subjects were proficient at performing the sequence, the cortical area innervating the contralateral long finger flexor and extensor muscles had increased by an average of 11%. This evidence of use-dependent plasticity at an early stage in the motor hierarchy is mirrored in a subsequent study in which TMS was used over the motor cortex to alter plasticity²². This time, the degree of plasticity was indexed by a greater degree of learning during performance of an implicit motor-learning task when TMS was applied over the motor cortex compared with application over a control site. Subjects performed a serial reaction-time task in which spatial cues, presented visually on a screen, indicated which key the subjects should press. Reaction times became shorter when, unknown to them, the visual cues were presented in sequence rather than randomly. Application of TMS at 10 Hz and at 1 Hz, respectively increased and decreased the amount of implicit learning that occurred. This

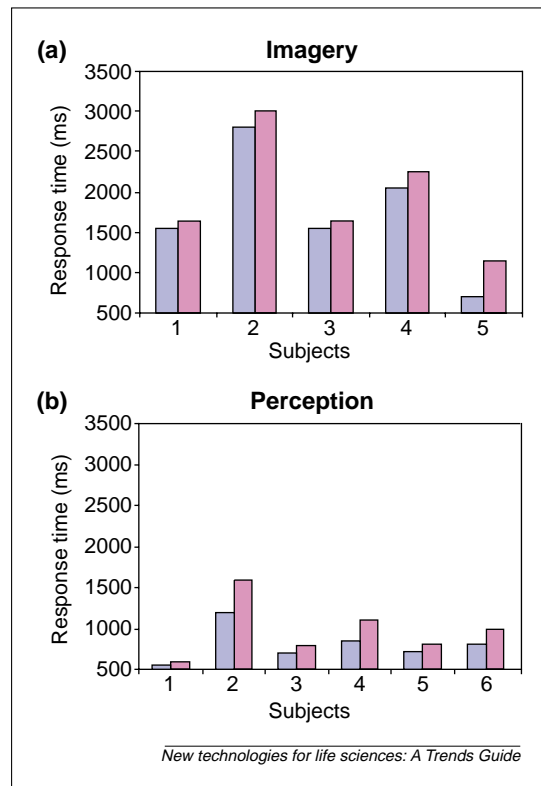


Figure 3. ‘Sham’ versus ‘real’ TMS

Comparison of ‘sham’ versus ‘real’ TMS delivered over occipital cortex while subjects performed a visual judgement task: (a) using visual imagery; or (b) by looking directly at the stimuli. Sham TMS (mauve bars) involves holding the coil over the target area but directing the field away from the cortex. Response times when real TMS was applied (pink bars) were always greater than when sham TMS was applied, both for the perception and the imagery condition. Adapted from Ref. 5.

rate-dependent plasticity has also been seen in the visual system²³. Once parametric studies have been conducted to ascertain the relevant rates of stimulation and the sensitivities of different cortical areas to such manipulations, this form of TMS may also hold therapeutic promise for the treatment of neurological disorders.

Catching the brain unaware

The first wave of TMS experiments predominantly used the technique to establish the function of the stimulated area. More recently, TMS has been used to look at the function of areas remote from, but connected to, the stimulated region. TMS applied over the occipital pole produces the percept of stationary phosphenes^{24,25} and TMS over V5 produces the percept of moving phosphenes²⁵. The capability of TMS to elicit phosphenes has recently been used to investigate whether cortical area V5 is sufficient to evoke a percept of motion in the absence of area V1 (Ref. 26). Subject GY, whose area V1 in the left hemisphere is almost completely destroyed, underwent extensive and intensive stimulation over the left occipital pole. No phosphenes were elicited. More surprisingly, TMS applied over GY’s intact left V5 also failed to produce any phosphenes, either stationary or moving, even though stimulation over V5 of the opposite hemisphere produced normal moving phosphenes. These findings suggest that area V1 is necessary for the perception of motion, and the anatomical connections between V5 and V1 suggest that the role of V1 in mediating such perception is likely to depend on back-projections from V5. This is currently the

object of a study that aims to disrupt the interaction by stimulating V1 soon after V5. Stimulating two areas close together in time is a development of TMS that has not been widely used in studies of cognition, but where there is a hypothesis regarding the relative timing of two cortical areas this dual-stimulation method can provide a means of testing temporal interactions.

Another look at seeing

The use of TMS need not always be driven by anatomy. Many of the findings from visual psychophysics, for example, are independent of anatomical constraints and often address functions that occur in spatially overlapping regions of cortex. Such psychophysical hypotheses are, however, still amenable to investigation with TMS. Some studies have already investigated visual masking²⁷, effects of luminance²⁸, topography²⁷ and motion²⁹, and the perceptual memory framework³⁰ opens up a new time window for experiments on psychophysical functions using TMS. The notion of perceptual memory proposes that memory for the visual attributes of a scene (colour, orientation, motion, contrast, etc.) is served by relatively low-level mechanisms beyond V1 but earlier in the processing hierarchy than the areas involved in object recognition. The prime candidate regions are therefore the secondary visual areas, at least one of which, V5, can be stimulated with TMS. Experiments based on this framework might be expected to apply TMS, not during the presentation of a stimulus, but after a to-be-remembered visual stimulus has been presented. As well as its use in the parametric study of the decay of the stimulus representation, applying TMS after stimulus presentation will also be useful in studies of visual priming.

Conclusion

The techniques in cognitive neuroscience occupy different spaces within which different types of questions can be asked (Fig. 2). In this overview, we have used a number of recent experiments to illustrate the nature of the problem space occupied by TMS. Of course, as Gandalf might have said, had he been addressing an audience of cognitive scientists, 'anyone who adopts a single technique to find out how the brain works strays from the path of wisdom'. The challenge we are left with is to recognize how the problem space occupied by the various techniques constrains the questions that can be asked of each.

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