Review

Magnetic stimulation studies of visual cognition

Vincent Walsh and Alan Cowey

The panoply of non-invasive techniques for brain imaging is responsible for much of the current excitement in cognitive neuroscience; sensory, perceptual and cognitive behaviour can now be correlated with cerebral blood flow as assessed by functional imaging, the electrical fields generated by populations of neurons or changes in magnetic fields created by electrical activity. Correlations between localized brain activity and behaviour, however, do not of themselves establish that any brain area is necessary for a particular task; necessity is the domain of the lesion technique. Transcranial magnetic stimulation (TMS) is a technique that can be used non-invasively to produce reversible functional disruption and has already been used to investigate visual detection, discrimination, attention and plasticity. The power of TMS as a 'lesion' technique lies in the opportunity to combine reversible disruption with high degrees of spatial and temporal resolution. In this review we trace some of the major developments in the use of TMS as a technique for the investigation of visual cognition.

Stimulation of the cerebral cortex as a means of revealing the localization of brain function has a long and successful history[1–3]. Comparable success can be claimed for the lesion method, which is important for establishing whether a particular brain region is necessary for a given behavioural accomplishment. With the development of transcranial magnetic stimulation (TMS) (see Box 1) as a technique for producing reversible functional impairments (or even improvements), cognitive neuroscientists now have the ability to study the effects of localized lesions and, because of the temporal specificity of TMS, to test hypotheses not only about spatial localization but also about the time course of mental processes. The study of visual cognitive processes with TMS is in its infancy, but the progress made so far suggests that it will play a leading part in establishing the functional roles of some of the cortical regions activated in neuroimaging studies, and also in reducing or even replacing the use of non-human primates in some types of lesion studies.

History

The fascinating history of magnetic stimulation can be found in many articles, but three detailed accounts are particularly useful[4–6]. An alarming case report of a young blind man who, in 1755, received a current through his head in a painful and unsuccessful attempt to restore his sight established that electrical stimulation could produce phosphenes[4] – sensations of light analogous to movements induced by stimulating motor cortex. Following the discovery of electromagnetic induction by Faraday and Henry it became possible to attempt to stimulate the nervous system painlessly by exposing subjects to changing magnetic fields. The first successful generation of magnetically induced phosphenes by d'Arsonval in 1896[4–6] was replicated by Beer in 1902 and later by Sylvanus Thompson in 1910. The problem for the induction and study of phosphenes was to generate a current of sufficiently high intensity and a rapid enough change of field strength to induce physiological activity in the brain – a non-trivial problem. Figure 1 shows one of the arrangements of coils devised to generate a magnetic field of sufficient strength to induce phosphenes[7,8].

By the late 1940s[9,10] it became clear that the phosphenes induced in earlier studies originated in the retina rather than the cortex. Following work on magnetic and electrical stimulation of isolated nerve fibres, the direct precursors to non-invasive magnetic stimulation were, firstly, the demonstration that the position of discrete phosphenes, evoked by direct electrical stimulation of the cortex, could be used to map the human primary visual cortex[11,12], and, secondly, the generation of cortically evoked phosphenes by non-invasive electrical stimulation[13]. A retinal cause of the phosphenes was precluded by inducing pressure ischaemia of the eyes[10]. The development of the stimulators that could produce the discharges required to generate a magnetic field sufficient to induce current in cortical tissue (see Box 1) soon followed and the current age of TMS began when Barker *et al.*[14] successfully stimulated human motor cortex in 1985.

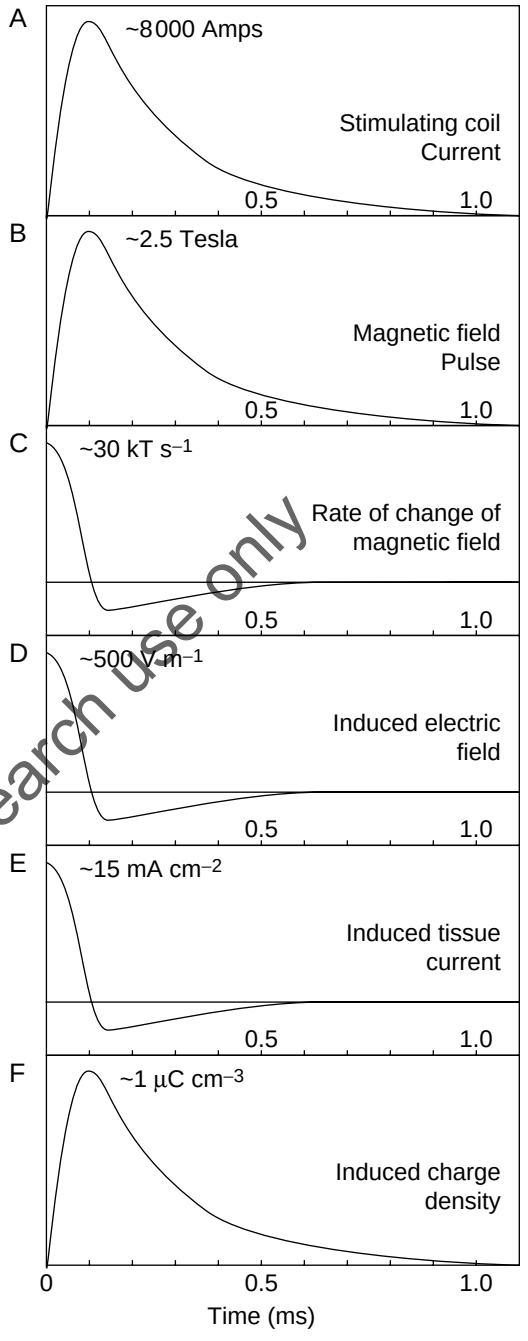
V. Walsh and A. Cowey are at the Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford, UK OX1 3UD.

tel: +44 1865 271326
fax: +44 1865 310447
e-mail: vincent.walsh @psy.ox.ac.uk

 1364-6613/98/$19.00 PII: S1364-6613(98)01134-6

Box 1. What is TMS?

Transcranial magnetic stimulation is the application of a brief magnetic pulse, or a train of pulses, to the scalp, which results in induction of a local electric field and, thus, TMS-induced changes in the local electrical field in the underlying surface of the brain. The modern age of magnetic stimulation began as recently as 1985 when Barker *et al.*[a] first stimulated the human motor cortex with a 2 Tesla pulse. Figure A traces the sequence of events (**A–F**) in the delivery of a single pulse. An electrical current of up to 8 kA is generated by a capacitor and discharged (**A**) into a circular or figure-of-eight shaped coil, which in turn produces a magnetic pulse of up to 2.5 Tesla. The pulse has a rise time of approximately 100 μs and a duration of 1 ms (**B**) and, owing to its intensity and brevity, changes at a rapid rate of around 30 kT s^{-1} (**C**). The changing magnetic field generates an electric field of some 500 V m^{-1} (**D**) that induces neural activity in the form of a tissue current of approximately 15 mA cm^{-2} (**E**). The net change in charge density in the cortex is zero after a small initial induced charge density (**F**). In addition to single pulse stimulation some simulators can deliver trains of pulses up to a rate of 50 Hz. Rapid-rate stimulation can induce seizures, so there is a trade-off between stimulus intensity and the rate of repetition. The exact area stimulated by the pulse and the depth of stimulation depends on several factors including coil shape[b–d] and whether the pulse is monophasic or biphasic.



References

a Barker, A.T., Jalinous, R. and Freeston, I.L. (1985) Non-invasive magnetic stimulation of human motor cortex *Lancet* 1, 1106–1107

b Jalinous, R. (1991) Technical and practical aspects of magnetic nerve stimulation *J. Clin. Neurophysiol.* 8, 10–25

c Jalinous, R. (1995) *Guide to Magnetic Stimulation*, The MagStim Company, Whitland, Wales

d Maccabee, P.J. *et al.* (1990) Spatial distribution of the electric field induced in volume by round and figure '8' magnetic coils: relevance to activation of sensory nerve fibers *Electroencephalogr. Clin. Neurophysiol.* 76, 131–141

Fig. The sequence of events in TMS. The panels **A–F** trace the sequence of events in the delivery of a single TMS pulse, and are described in the text. The details of the electric current in the stimulating coil and the subsequent effects on neural tissue are taken from Ref. c and are calculated for the MagStim 200 with a 70 mm circular coil.

Pioneering studies

The development of TMS as an investigative tool depended substantially on investigations of functions of the motor cortex. These resulted from the accessible dorsolateral aspect of the motor cortex, our detailed knowledge of the motor homunculus and the consequent ability to use motor 'hot spots' (points on the scalp at which the thresholds for eliciting an electromyogram are lowest) and recordings from distal muscles as markers of localization[15–17]. Work on the visual system developed more slowly and until recently was concerned with localization of the sites most likely to elicit phosphenes[4].

The watershed in using TMS to study visual cognition occurred in 1989 in a study that demonstrated that TMS could be used, in its disruptive mode, in conjunction with paradigms from classical experimental psychology. Amassian *et al.*[18] delivered single-pulse TMS over the occipital cortex of subjects performing a letter-identification task (see Fig. 2). Performance was impaired when TMS was applied between 60 and 140 ms after the onset of the presentation of the stimuli, and when it was applied between 80 and 100 ms after stimulus onset subjects were incapable of detecting any of the letters. This result was soon replicated and correlated with visually evoked potential (VEP) latencies in clinically normal and abnormal subject groups[19].

Amassian and colleagues also took their experiment a significant stage further by showing that TMS could unmask a visual mask (i.e. like disinhibition) and thus improve

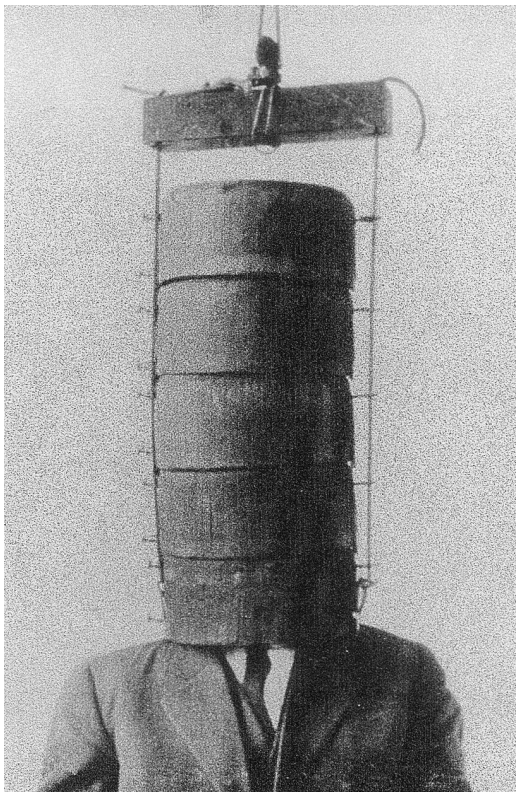


Fig. 1 Size matters. Early attempts to induce phosphenes by brain stimulation suffered from the difficulties of producing the requisite large, rapidly-changing electromagnetic fields. Here we see the arrangement of coils used by Magnussen and Stevens[8,9]. Coils were piled upon one another to create the increase in field strength. (Reproduced, with permission of Taylor & Francis, from the Philosophical Magazine, Ref. 8.)

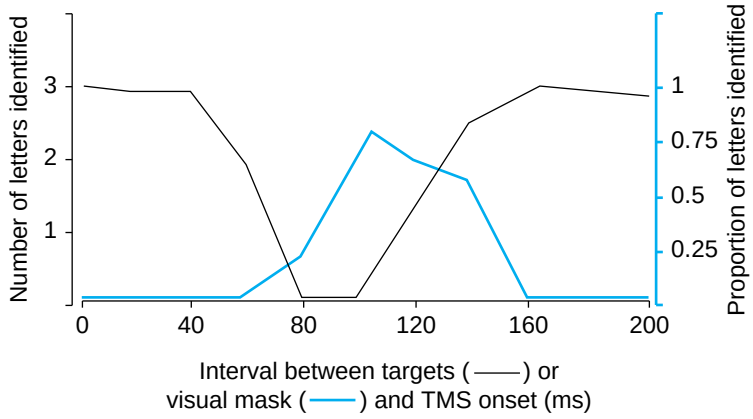


Fig. 2 The effects of TMS on detection of trigrams. The black line (ordinate on the left representing the number of letters correctly identified in trigrams) shows the effects of TMS on recognition. When TMS was applied at 0–40 ms after the onset of the presentation of the letters there was virtually no effect of TMS on recognition. But TMS applied between 60 and 140 ms after stimulus onset impaired performance and reduced recognition to zero between 80 and 100 ms. The blue line (ordinate to the right showing the proportion of letters correctly identified in the presence of a visual mask) resembles the inverse of the recognition paradigm. (Redrawn from Refs 18 and 20.)

performance[20]. In the latter experiment, subjects were presented with the same letter-identification arrays, followed 100 ms later by a high-contrast visual mask, and single-pulse TMS was applied at various intervals after the presentation of the mask. The effect of TMS was to prevent the presentation of the first stimulus (the mask) from impeding identification of the second stimulus, as occurred without TMS. Figure 2 shows the reciprocal effects of TMS in the two experiments.

In these two experiments lies the foundation for all subsequent studies of visual cognition using TMS: one can either impair visual performance by interfering with the transmission of relevant visual signals or one can improve performance by interfering with the transmission of irrelevant or competing stimuli.

How cognitive is cognitive?

That one can disrupt or enhance performance in a cognitive task does not necessarily mean that the cause of the behavioural change is cognitive in nature, and the early work accordingly led to two strands of enquiry in TMS research, which might be described as sensory and cognitive. Two examples of the former, concentrating on changes in threshold sensitivity following TMS, raise the question of the extent to which apparently cognitive effects can be explained in terms of sensitivity changes.

First, Miller *et al.*[21] showed that decreasing the luminance of a target, and thus increasing the time needed to process it, resulted in longer latencies for TMS effects. Apart from validating the utility of TMS in studying the time course of visual processing, this also highlights the importance of low-level information in visual experiments and may explain a source of timing differences between different studies. Kammer and Nusseck[22] on the other hand argue explicitly that visual suppression effects can be interpreted as a change in visual contrast threshold.

An alternative approach to this question is to attempt to localize the exact site at which TMS suppresses vision[23,24] and ask whether this is consistent with a sensory analysis of results or requires some more cognitive explanation. Epstein *et al.*[24] took this approach and on the basis of localization of induced currents, argue that attentional effects may need to be considered when explaining effects that appear sensory in nature.

Creating virtual patients

The second strand of research that sprang from Amassian *et al.*'s success is exemplified by a number of studies that attempted to mimic the effects of neurological lesions. The contemporary use of TMS as a tool in vision research is best understood as a pulsatile lesioning technique and the rationale of analysis is the same as that applied to neuropsychological studies of the effects of lesions in neurological patients or in monkeys.

Visual extinction is a common phenomenon following damage to the parietal cortex, particularly damage in the right hemisphere. Patients who can report the identity of a single stimulus presented in either the right or the left visual hemifield nevertheless fail to see the stimulus presented in the field contralateral to the lesion when it is accompanied by one in the ipsilateral field[25]. In their pioneering study Pascual-Leone *et al.*[26] used repetitive-pulse TMS (rTMS) over the occipital, temporal or parietal cortices and, as shown in Figure 3, TMS over the parietal cortex increased errors in the bilateral but not unilateral presentation condition. Their investigation employed rTMS rather than

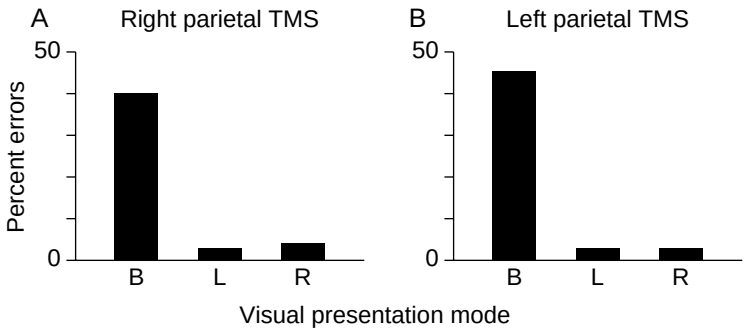


Fig. 3 Visual extinction produced by TMS. When two stimuli are presented simultaneously, one in each hemifield (indicated as B on the abscissae), TMS over the parietal lobe of either right **(A)** or left **(B)** hemisphere reduces detection of the stimulus in the contralateral visual field to chance levels. Detection is not reduced with presentation of a single stimulus to one hemifield (indicated as L or R on the abscissae). (Redrawn from Ref. 26.)

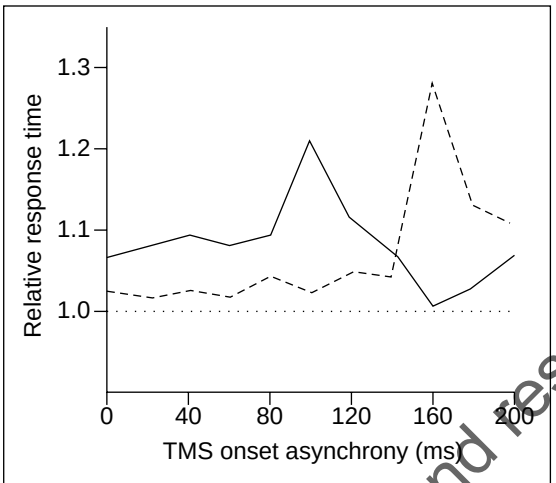


Fig. 4 The effects of TMS applied to the parietal cortex during visual search. The dotted line at 1.0 on the ordinate indicates the control reaction time in the absence of TMS. The solid line that peaks at 100 ms represents reaction time relative to control trials, when a target was present; the dashed line that peaks at 160 ms represents reaction time relative to control trials when the target was absent. (See Ref. 29 for full details.)

single-pulse TMS because of early difficulties in achieving visual cognitive effects with single pulses. Other cognitive functions have been shown to be resistant to single-pulse stimulation and Pascual-Leone *et al.*[27] originally showed this in the induction of speech arrest. One explanation of this resistance of cognitive events to single-pulse TMS (suggested by a referee of this article) is that cognitive processes 'might be processed through parallel pathways and with sufficient re-entry mechanisms that repetitive stimuli (rTMS) are required to block them.' Indeed, the visual system possesses a great deal of redundancy, the effects of which are seen repeatedly in the recovery of monkeys from visual cortex lesions, and which can be exploited during recovery from brain damage.

The cost of using rTMS rather than single-pulse TMS is, of course, the diminution of temporal resolution, so it became important to devise a method of using single-pulse TMS to disrupt activity in higher cortical areas. In their earlier studies (e.g. Refs 26,27) Pascual-Leone *et al.* had used an all-or-none response paradigm (subjects were either correct or they were not) but the deficits of neuropsychological patients and monkeys with brain lesions are customarily measured in terms of elevated thresholds or increases in reaction time; that is, by continuous rather than discrete measures. Seyal *et al.*[28] used single-pulse TMS to examine changes in sensory thresholds (a continuous measure) for detection of a tactile stimulus and found that detection thresholds were significantly elevated when using the hand contralateral to magnetic stimulation if it was applied to the parietal lobe 50 ms before the tactile stimulation. Signally, the effect was asymmetric in that sensitivity with the hand ipsilateral to magnetic stimulation was actually enhanced. Again, the ability of TMS specifically to enhance performance and to mimic the effects of neurological lesions is evident. Following this experiment we employed single-pulse TMS over the parietal cortex while subjects performed visual search tasks[29]. TMS had no detrimental effects on performance measured as correct responses (target present versus target absent) but by using a continuous dependent variable (reaction time) large and specific effects emerged. TMS applied over the right dorsolateral parietal cortex significantly slowed responses on visual search tasks that were performed serially but not those that could be performed pre-attentively. This might have been just another replication of the performance of neuropsychological patients[30] but the critical time of TMS depended on whether a target was present or absent (Fig. 4), something not observed in patients. Using continuous measures, then, and with the high temporal resolution of TMS, it is possible to go beyond the findings of neuropsychological studies.

Functional specialization

One of the most important concepts in understanding visual function is that of functional specialization[31]. The experiments discussed so far were inspired and driven by psychological theory or findings from studies of neuropsychological patients, but none could be said to have addressed questions of functional localization. If a technique is to make a new contribution to a field, a good test of its utility is to attempt to delineate questions within a paradigm currently in use, such as the functional specialization of vision. Several studies[32–35] have examined the effects of TMS directed at human visual area V5 (equivalent to monkey MT or middle temporal cortex) (see also Box 2), a region known to be important for aspects of visual motion perception, but two are of particular cognitive interest.

While subjects performed motion-direction discrimination tasks, single-pulse TMS was applied over the left extrastriate cortex[35]. As one might expect, TMS elevated discrimination thresholds, but it did so in *both* visual hemifields, which was contrary to expectations based on single unit receptive-field data and on previous studies that failed to obtain any effects of TMS ipsilateral to the hemifield in which the stimuli were presented[34]. As Hotson *et al.*[35] noted, V5 has transcallosal homotopic connections, and interhemispheric effects have also been observed following motor cortex stimulation. Perhaps unilateral stimulation has bilateral physiological effects. Support for this explanation comes from two studies that combined TMS with positron emission tomography (PET)[36] and electro-encephalography (EEG) recording[37], respectively. The combination of TMS

Box 2. Methodological issues in TMS

Localization of stimulation

TMS is sometimes reported to have been applied to a particular cortical area (for example, area V5 in a recent study[a]) but it is clear from studies of blood flow[b] or electrical activity[c] following TMS that the physiological effects of stimulation are not restricted to the small region at which one is aiming. There is a spread of effects to physically nearby areas[c] and to areas that are anatomically connected[b]. Several steps can be taken to improve localization. It is preferable, for example, to base the selection of stimulation sites on MRIs of the subjects' brains rather than on EEG scalp electrode coordinates. The choice of coil shape will also influence localization[d].

Anatomical pin-pointing is only one goal, however, and where the hypothesis is functional (i.e. aims to partition the components of a cognitive process in time rather than localize them in space) it is sufficient to demonstrate temporal specificity without addressing anatomical specificity. The best example of this is perhaps the early body of work by Amassian and colleagues (see main text).

The logic of lesion analysis is also important in assessing localization. We can take the study of V5 and motion perception as a case study. For example, if there is an effect on motion perception following TMS over V5 (Refs a,e), and the effect is specific to stimulation within a 1 cm region of the scalp, then one may be confident that the effects were not due to the kind of spreading of effect seen in the first two frames of Figure 5 (main text). Further, if control stimulations are then applied to another site, say the parietal cortex to which V5 projects, and the effect on motion perception is not obtained, one can be more confident that the results are not due to TMS effects on areas anatomically connected to the site at which TMS was applied[b]. To ensure that the effects are specific to tasks involving motion one can also apply TMS over V5 during non-motion tasks to establish a functional, rather than an anatomical dissociation.

Peripheral effects

When TMS is delivered close to the scalp it produces a pronounced click or tapping sensation and the stimulation of facial nerves often produces slight muscle twitches, including eyeblinks. These effects are time-locked with the magnetic pulse and could therefore influence sensory and cognitive performance. The resolution of this problem is similar to that of localization. Stimulation at a control site near to the site of interest usually reproduces the unwanted effects of TMS and thus provides a control. Other measures that have been used to control for these unwanted confounds are: direct stimulation of the facial nerve, to produce facial twitches and eye blinks; task dissociation – if TMS impairs performance on one task but improves it on another it is difficult to construct an explanation in terms of a non-specific artefact; when stimulating at control sites use a higher intensity of TMS, i.e. produce a greater artefact at the control site.

Duration of effects

One of the attractions of TMS is the apparent precise temporal resolution in the context of a 'lesion' or disruption of function. However, we have very little understanding of the longevity of the effects of TMS. Figure 5 (main text) shows clearly that the effects may last for up to 10 ms at the site of stimulation but effects in anatomically connected regions can be seen at least 30 ms after stimulation when subjects are not performing any task. So how do we account for the time specificity (often in the range of 10–20 ms) reported in many experiments? One can speculate that during performance of a task, the 'recovery' from TMS is swifter than 30 ms due to the coordinated activity in other regions involved in the task; it would be interesting to see this tested with the paradigm used by Ilmoniemi *et al.*[c] Another possibility is that TMS is more likely to disrupt a function if applied at a particular time before the crucial neuronal operations have begun. A precedent for this is seen in the failure of TMS to disrupt saccades unless the pulse is applied approximately 100 ms before onset[f]. Nevertheless, our lack of knowledge concerning the duration of TMS effects remains an important issue to be resolved.

References

a Walsh, V. *et al.* (1998) Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5 *Proc. R. Soc. London Ser. B* 265, 1–7

b Paus, T. *et al.* (1997) Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex *J. Neurosci.* 17, 3178–3184

c Ilmoniemi, R.J. *et al.* (1997) Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity *NeuroReport* 8, 3537–3540

d Maccabee, P.J. *et al.* (1990) Spatial distribution of the electric field induced in volume by round and figure '8' magnetic coils: relevance to activation of sensory nerve fibers *Electroencephalogr. Clin. Neurophysiol.* 76, 131–141

e Hotson, M. *et al.* (1994) Transcranial magnetic stimulation of extrastriate cortex degrades human motion direction discrimination *Vis. Res.* 34, 2115–2123

f Zangmeister, W.H., Canavan, A.G.M. and Hoemberg, V. (1995) Frontal and parietal transcranial magnetic stimulation (TMS) disturbs programming of saccadic eye movements *J. Neurol. Sci.* 133, 42–52

and PET revealed that TMS increased regional cerebral blood flow in several areas ipsilateral, and some contralateral, to the site of stimulation (in this case the frontal eye fields). The TMS–EEG study provided more direct evidence for transcallosal effects in the occipital lobe (Fig. 5).

A more recent study of the effects of TMS applied over area V5 has revealed not only that V5 is important for motion perception in a visual search paradigm but also that disruption of V5 during performance of non-motion search tasks can actually improve performance[32]. This indicates that different visual areas may normally compete with each other (for example, by inhibition during selective attention) and that disorganizing one area may disinhibit others. Again, this is not something one could easily infer from studies of neurological patients. There are many examples of paradoxical improvements following brain damage[38] but the well-known patient 'L.M.', who is impaired on visual search tasks that require attention to motion, does not show any improvement on tasks that do not require motion processing[39]. Thus, because of the short-term and reversible nature of the lesions induced, TMS can capture effects that perhaps are masked by reorganization following irreversible brain damage.

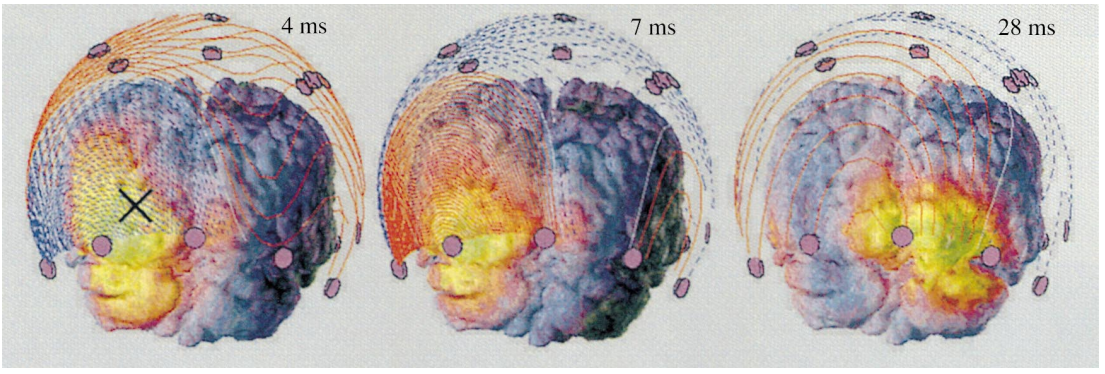


Fig. 5 Duration of changes in neural activity induced by TMS. Four ms after TMS over the occipital lobe most of the electrical activity recorded with high resolution EEG is around the area directly under the TMS stimulation site (marked by the ×). By 7 ms this has spread to the midline and by 28 ms there is clearly contralateral activation. (Reproduced, with permission of Oxford University Press, from Ref. 37.)

The effects of TMS over V5 cannot be correlated with a simple increase or decrease in cortical activity; rather, they should be understood as the result of adding noise to the visual motion system. A quite different effect, which has clear implications for cognitive studies using TMS, was reported by Tarazona *et al.* (*Soc. Neurosci. Abstr.* 23, p. 1964). Repetitive-pulse TMS was applied to the motor cortex at either 1 or 10 Hz during learning of a serial reaction-time task, and implicit learning of the task was correlated with a measure of cortical excitability. The 1 Hz stimulation, which decreased excitability, correlated with a decrease in implicit learning whereas the 10 Hz stimulation increased both excitability and implicit learning. This kind of specificity has not yet been demonstrated in visual cognition but may have applications in visual learning and memory experiments.

Plasticity

One of the major drawbacks with the lesion method is that the lesion is usually permanent (unless cooling or reversible chemical lesions are used). It follows that investigations of patients with brain damage or monkeys with aspiration lesions are, in an important sense, studies of brains that may have reorganized to perform a task by abnormal means. Thus, as a subject improves on a task one can never be sure whether the task is being performed as it would be with practice by an intact brain or whether one is studying a reorganized system. TMS has already proved useful in two ways here: it has been used to study the effects of abnormal reorganization[40] and to examine normal changes in cortical organization as a consequence of learning a visual task[41]. In subjects blind from birth it has been shown that blood flow changes can occur in the primary visual cortex in response to tactile input[42] but whether this is functionally useless activity following random recruitment of neurons deprived of a visual input, or a functionally relevant change was previously open to question. Using rTMS Cohen *et al.*[40] were able to disrupt tactile information-processing by stimulating the occipital cortex of blind subjects but not of sighted subjects. If the activity in visual cortex of the blind subjects were merely aberrant neural noise in the system then disrupting it should not have impaired tactile perception. Thus, the authors demonstrated that the correlational data from the earlier neuroimaging study[42] did reflect an adaptive functional reorganization. A similar study might demonstrate a corollary in cortical reorganization in the congenitally deaf[43].

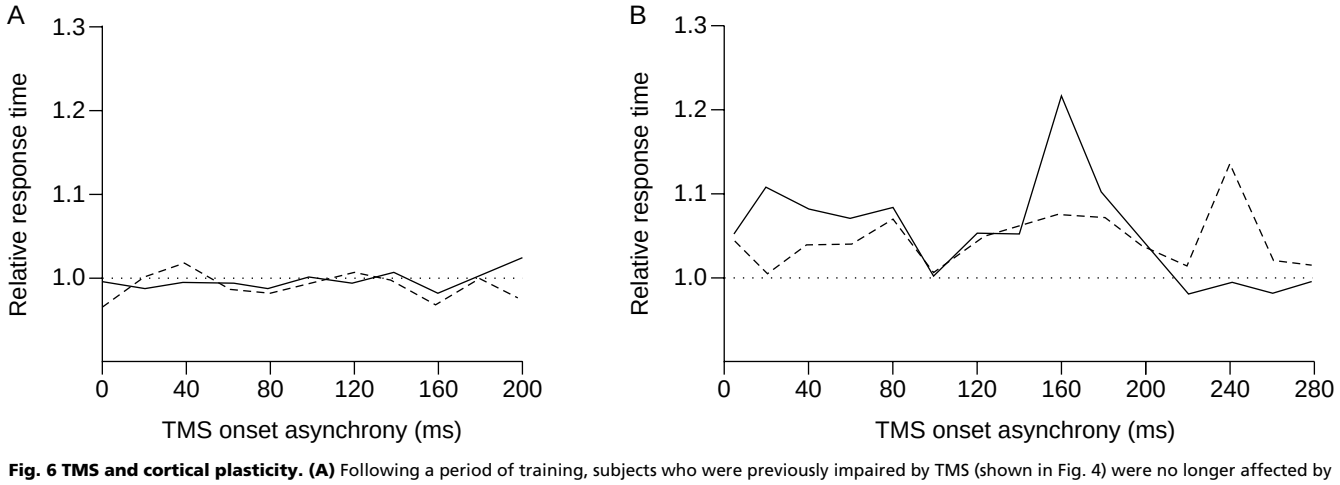


Fig. 6 TMS and cortical plasticity. (A) Following a period of training, subjects who were previously impaired by TMS (shown in Fig. 4) were no longer affected by TMS and the reaction times with TMS (solid and dashed lines) did not differ from those on control trials (dotted line). **(B)** When the same subjects were introduced to a new visual search task the effects of TMS over parietal cortex returned, indicating that learning is stimulus specific. (See Ref. 41 for full details.)

Box 3. Safety and ethical issues in TMS

Magnetic stimulators induce magnetic fields, produce an audible noise, muscular twitches and can apply pulses at different temporal rates. Each of these presents an issue of ethics or safety.

Jalinous[a] notes the importance of taking generalized precautions when dealing with electromagnetic fields. Thus floppy discs, credit cards, computers and computer screens should be kept reasonably distant – in our laboratory we keep any materials that might be affected more than one metre away from the coil. Any form of medical implant, for example a pacemaker, should not be brought within the vicinity of an operating stimulator.

The audible noise (a sharp crack) from the coil can reach over 100 dB and be uncomfortable. However, few experiments ever require use of the full power of the stimulators and the use of earplugs markedly reduces the discomfort and prevents any short-term changes in acoustic thresholds[b]. Facial twitches are another source of potential discomfort. For these or any other source of discomfort, it is important to allow subjects to opt out of the experiment at any time they so wish.

It is widely agreed that, with simple precautions, single pulse TMS has no deleterious effects either in the short or long term[c] although Bridgers[d] correctly cautions against the use of TMS in any subject one might suspect is susceptible to adverse effects (for example, a personal or family history of epilepsy precludes participation in our experiments). Repetitive pulse stimulation (rTMS) carries a small risk of inducing a seizure. Pascual-Leone *et al.*[b] carried out an extensive study of the effects of different temporal rates of rTMS and pulse intensity (measured as a percentage of motor threshold) and their study now forms the basis of guidelines adopted by many using rTMS. Although rTMS appeared not to produce effects on performance in general neuropsychological tests, cognitive performance, EEG, ECG or several measures of hormone levels, it is possible that their results are valid only for the specific sites stimulated – (i) motor cortex, (ii) 5 cm anterior, and (iii) 5 cm posterior to motor cortex – and that new guidelines may have to emerge for rTMS in the visual system. It is also worth noting that Pascual-Leone *et al.* administered pulses in trains 10 s long: in experiments on visual cognition it is unlikely that rTMS will need to be used in trains longer than one second.

One final ethical consideration is the potential of TMS to help reduce or replace the use of non-human primates in lesion experiments. Because of the rapidly and repeatedly reversible and non-invasive nature of the disruption caused by TMS it will be possible to use monkeys as their own controls in experiments using TMS. Some studies have already shown that TMS can be used to good advantage in non-human primates (for example, see Ref. e), but it is an area in which much remains to be explored. As a better understanding of the effects of TMS in the human visual system is obtained, it is not difficult to anticipate that many questions that would once have required lesions in a group of primates (for example, whether cortical visual area V5 is important for detection of either first or second order motion) will be amenable to an experiment using TMS in normal human volunteers.

References

a Jalinous, R. (1995) *Guide to Magnetic Stimulation*, The MagStim Company, Whitland, Wales

b Pascual-Leone, A. *et al.* (1993) Safety of rapid-rate transcranial magnetic stimulation in normal volunteers *Electroencephalogr. Clin. Neurophysiol.* 89, 120–130

c Chokroverty, S. *et al.* (1995) Magnetic brain stimulation: safety studies *Electroencephalogr. Clin. Neurophysiol.* 97, 36–42

d Bridgers, S.L. (1991) The safety of transcranial magnetic stimulation reconsidered: evidence regarding cognitive and other cerebral effects, in *Magnetic Motor Stimulation: Basic Principles and Clinical Experience* (EEG Suppl. 43) (Levy, W.J. *et al.*, eds), pp. 170–179, Elsevier

e Flament, D., Hall, E.J. and Lemon, R.J. (1992) The development of corticomotorneuronal projections investigated using magnetic brain stimulation in the infant macaque *J. Physiol.* 447, 755–768

Plasticity in neurologically intact individuals was examined in a perceptual learning experiment in which subjects received TMS over the right parietal lobe during a visual search task (see Fig. 4). Following extensive training on the task until the character of their performance had changed the subjects again received TMS over the same cortical site, when the effect disappeared (see Fig. 6A). The subjects were then transferred to a new visual search array and again received TMS. Their performance returned to pre-training standards and the effect of TMS was reinstated (Fig. 6B), suggesting that TMS had initially disrupted a stimulus-specific process[44].

Conclusions

TMS is a young, but already well-established, 'lesion' or 'stimulation' technique that can be used to test the findings of brain imaging studies and neuropsychological investigation (the safety and ethical issues surrounding the technique are discussed in Box 3). More importantly, however, TMS can address questions outside the domain of other techniques because of its combination of spatial and temporal resolution, not available with any other lesion technique. The use of continuous variables enhances the sensitivity of the technique. Further, as it becomes more common to establish the sites of stimulation by anatomical MRI and to combine TMS with other imaging techniques[36,37], we will also be able to build a more accurate picture of which cortical brain regions are necessary for different components of visual behaviour.

Acknowledgements

Some of the work reported here was supported by MRC Grants G971/397/B and ROPA G9711247, the EC Human Capital and Mobility Program, the Forbairt trust, The McDonnel-Pew Foundation and The Royal Society.

References

1 Ferrier, D. (1876) *The Functions of the Brain*, Smith Elder

2 Fritsch, G. and Hitzig, G. (1870) Uber die elektrische Erregbarkeit des Grosshirns *Arch. Anat. Physiol. Wiss. Med.* 37, 300–332 (English translation in von Bonin, G., 1960, *Some Papers on The Cerebral Cortex*, pp. 73–96, Thomas, Springfield Illinois)

3 Penfield, W. and Boldrey, E. (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation *Brain* 60, 389–443

4 Marg, E. (1991) Magnetostimulation of vision: direct non-invasive stimulation of the retina and the visual brain *Optom. Vis. Sci*. 68, 427–440

5 Geddes, L.A. (1991) History of magnetic stimulation of the nervous system *J. Clin. Neurophysiol*. 8, 3–9

6 Geddes, L.A. (1989) The history of stimulation with eddy currents due to time-varying magnetic fields, in *Magnetic Stimulation in Clinical Neurophysiology* (Chokroverty, S., ed.), pp. 5–11, Butterworth

7 Magnussen, C.E. and Stevens, H.C. (1911) Visual sensation caused by changes in the strength of a magnetic field *Am. J. Physiol*. 29, 124–136

8 Magnussen, C.E. and Stevens, H.C. (1914) Visual sensation caused by a magnetic field *Philos. Mag*. 28, 188–207

9 Walsh, P. (1946) Magnetic stimulation of the human retina *Fed. Proc*. 5, 109–110

10 Barlow, H.B., Kohn, H.I. and Walsh, E.G. (1947) Visual sensations aroused by magnetic fields *Am. J. Physiol*. 148, 372–375

11 Brindley, G.S. and Lewin, W.S. (1968) The sensations produced by electrical stimulation of the visual cortex *J. Physiol*. 196, 479–493

12 Brindley, G.S. *et al*. (1972) The extent of the region of the occipital cortex that when stimulated gives phosphenes fixed in the visual field *J. Physiol*. 225, 57–58

13 Merton, P.A. and Morton, H.B. (1980) Electrical stimulation of the human motor and visual cortex through the scalp *J. Physiol*. 305P, 9–10

14 Barker, A.T., Jalinous, R. and Freeston, I.L. (1985) Non-invasive magnetic stimulation of human motor cortex *Lancet* 1, 1106–1107

15 Mills, K.R. (1991) Magnetic brain stimulation: a tool to explore the action of the motor cortex on single human spinal motor neurones *Trends Neurosci*. 14, 401–405

16 Day, B.L. *et al*. (1989) Electric and magnetic stimulation of the human motor cortex: surface EMG and single motor unit responses *J. Physiol*. 412, 449–473

17 Rothwell, J.C. (1993) Evoked potentials, magnetic stimulation studies, and event-related potentials *Curr. Opin. Neurobiol*. 6, 715–723

18 Amassian, V.E. *et al*. (1989) Suppression of visual perception by magnetic coil stimulation of human occipital cortex *Electroencephalogr. Clin. Neurophysiol.* 74, 458–462

19 Masur, H., Papke, K. and Oberwittler, C. (1993) Suppression of visual perception by transcranial magnetic stimulation: experimental findings in healthy subjects and patients with optic neuritis *Electroencephalogr. Clin. Neurophysiol.* 86, 259–67

20 Amassian, V. E. *et al*. (1993) Unmasking human visual perception with the magnetic coil and its relationship to hemispheric asymmetry *Brain Res*. 605, 312–316

21 Miller, M.B. *et al*. (1996) Transcranial magnetic stimulation: delays in visual suppression due to luminance changes *NeuroReport* 7, 1740–1744

22 Kammer, T. and Nusseck, H.G. Transcranial magnetic stimulation over visual cortex raises contrast thresholds in humans *Neuropsychologia* (in press)

23 Epstein, C. and Zangaladze, A. (1996) Magnetic coil suppression of extrafoveal visual perception using disappearance targets *J. Clin. Neurophysiol*. 13, 242–246

24 Epstein, C., Verson, R. and Zangaladze, A. (1996) Magnetic coil suppression of visual perception at an extracalcarine site *J. Clin. Neurophysiol*. 13, 247–252

25 Bisiach, E. (1991) Extinction and neglect: same or different?, in *Brain and Space* (Paillard, J., ed.), pp. 251–257, Oxford University Press

26 Pascual-Leone, A. *et al*. (1994) Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe *Neurology* 44, 494–498

27 Pascual-Leone, A., Gates, J.R. and Dhuna, A. (1991) Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation *Neurology* 41, 697–702

28 Seyal, M., Ro, T. and Rafal, R. (1995) Increased sensitivity to ipsilateral cutaneous stimuli following transcranial magnetic stimulation of the parietal lobe *Ann. Neurol.* 38, 264–267

29 Ashbridge, E., Walsh, V. and Cowey. A. (1997) Temporal aspects of visual search studied by transcranial magnetic stimulation *Neuropsychologia* 35, 1121–1131

30 Arguin, M., Joanette, Y. and Cavanagh, P. (1993) Visual search for feature and conjunction targets with an attention deficit *J. Cogn. Neurosci.* 5, 436–452

31 Zeki, S. (1993) *A Vision of the Brain*, Blackwell Scientific

32 Walsh, V. *et al*. (1998) Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5 *Proc. R. Soc. London Ser. B* 265, 1–7

33 Beckers, G. and Homberg, V. (1992) Cerebral visual motion blindness: transitory akinetopsia induced by transcranial magnetic stimulation of human area V5 *Proc. R. Soc. London Ser. B* 249, 173–178

34 Beckers, G. and Zeki, S. (1995) The consequences of inactivating areas V1 and V5 on visual motion perception *Brain* 118, 49–60

35 Hotson, M. *et al*. (1994) Transcranial magnetic stimulation of extrastriate cortex degrades human motion direction discrimination *Vis. Res.* 34, 2115–2123

36 Paus, T. *et al*. (1997) Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex *J. Neurosci*. 17, 3178–3184

37 Ilmoniemi, R.J. *et al*. (1997) Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity *NeuroReport* 8, 3537–3540

38 Kapur, N. (1996) Paradoxical functional facilitation in brain-behaviour research: a critical review *Brain* 119, 1775–1790

39 Zihl, J., von Cramon, D. and Mai, N. (1983) Selective disturbance of movement vision after bilateral brain damage *Brain* 106, 313–340

40 Cohen, L.G. *et al*. (1997) Functional relevance of cross-modal plasticity in blind humans *Nature* 389, 180–183

41 Walsh, V., Ashbridge, E. and Cowey, A. (1998) Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation *Neuropsychologia* 36, 45–49

42 Sadato, N. *et al*. (1996) Activation of primary visual cortex by Braille reading in blind subjects *Nature* 380, 526–528

43 Neville, H.J. (1990) Intermodal competition and compensation in development: evidence from studies of the visual system in congenitally deaf adults, in *The Development and Neural Basis of Higher Cortical Development: Comparative and Cross-Cultural Perspectives* (Diamond, A., ed.), pp. 127–143, New York: Aldine Gruyter Press

44 Ellison, A. and Walsh, V. (1998) Perceptual learning in visual search: some evidence of specificities *Vis. Res*. 38, 333–345