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REVIEW

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Transcranial magnetic stimulation studies of cognition: an emerging field

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Abstract In this short review, we consider the application of transcranial magnetic stimulation (TMS) to the study of cognitive function. Following an introduction to the technique, we consider its possible mechanisms of action. We then review the studies that have applied TMS to the investigation of cognition. In the majority of these investigations, TMS has been applied to disrupt function and demonstrate that a particular cortical area is essential for performance of the task under study. Finally, we highlight pertinent design and procedural issues and consider other types of questions that can be addressed by future TMS studies of cognitive function.

Key words Transcranial magnetic stimulation · Cognition

Introduction

Transcranial magnetic stimulation (TMS) is a method of delivering electrical stimuli to the brain through the intact scalp. Unfortunately for neuroscientists, the scalp and skull have a high resistance to electrical current, which makes it difficult for conventional electrical stimuli to penetrate into the brain. Magnetic stimulation works by inducing a large, rapidly changing magnetic field in the neighbourhood of a small coil of wire held over the scalp. The skull has no impedance to the passage of a magnetic field and it passes readily into the brain. Because the field changes so rapidly, it induces electrical currents in the brain. Depending on the make of the stimulator used, the currents last for 100–500 μs. This time course is similar to that produced by conventional electrical peripheral-nerve stimulation. Despite its name, the magnetic part of the transcranial magnetic stimulus has no role in stimulation; the magnetic field simply carries an electrical stimulus across the scalp and skull.

For the first five years after its introduction in 1985 (Barker et al. 1985), TMS was mainly used to explore the motor cortex. The reason for this was that the effects of motor-cortex stimulation are easy to observe and quantify. Because the motor cortex has a large and direct projection to the spinal cord, each single stimulus can evoke a visible muscle twitch, which can be recorded with electromyograph (EMG) equipment. With such a simple response measure, it was easy to study corticospinal conduction times, to quantify the effects of stimulus intensity or stimulus polarity, and to measure the focality of stimulation.

There are three general features of those results that are probably applicable to all areas of cortex (see Rothwell et al. 1991). First, a given intensity of stimulation has a greater effect when applied during activity than at rest. This is because a magnetic stimulus evokes synaptic activity in the cortex, and this has a greater effect on post-synaptic neurones if they are active when the stimulus is given. Second, stimulation is not very focal. Indeed, physical principles show that electrical currents are induced in an area that is at least as large as the coil used to stimulate. A common way to get around this problem is to wind coils into a figure of eight shape so that the field under the junction region of the coil is twice that under the two loops. Relying on the fact that neurones usually have a threshold for stimulation, we can usually assume that, over a given range of intensities, stimulation is limited to sites under the junction region. However, subthreshold effects undoubtedly occur under all parts of the coil. The lack of certainty about the area of cortex activated by a coil does not necessarily limit the accuracy of cortical mapping. Since the stimulus has a peak value at a defined position(s) under the coil and

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then falls off with distance, it is still possible to plot the "best point" for stimulation with some accuracy. For example, in the motor cortex, it is possible to distinguish separate "best points" for individual forearm and hand muscles, even if only 0.5 cm or so separates them (Wassermann et al. 1992; Byrnes et al. 1998**)**. This does not mean that the area affected by the stimulus is limited to a range of 0.5 cm from the coil, only that the point of maximum stimulus is limited to that area.

The third general feature to note about TMS is that orientation of the coil on the scalp can influence which elements in cortex are activated by a given intensity of stimulation. For example, in the motor cortex, stimulating currents that flow from posterior to anterior across the central sulcus evoke EMG responses that have a latency that is sometimes 2–3 ms longer than responses evoked by currents induced in the opposite direction (by reversing the orientation of the coil) **(**Day et al. 1989**)**. Clearly, different current directions stimulate different neural elements in the cortex. The reason is thought to relate to the homogeneity of the electrical currents that TMS can induce. For physical reasons, currents induced by TMS only flow parallel to the surface of the brain; there is no component of radial flow (Tofts 1990). Because (1) neurones are excited best by longitudinal rather than transverse currents, and (2) cortical neurones are arranged in particular orientations with respect to the surface of the brain, this means that TMS can preferentially activate specific populations of cortical neurones (Amassian et al. 1992b). Conventional electrical stimulation almost invariably produces some component of radial current and, therefore, is much less selective in this respect.

The application of TMS to other areas of cortex has been much slower than for the motor areas. This is not because of any intrinsic problem of stimulating other areas of brain, but because of difficulties in quantifying the effect of stimulation. The primary visual cortex was the second area to be studied in any detail. Stimulation here can evoke phosphenes in the visual field in a manner reminiscent of the muscle twitches evoked by stimulation of primary motor cortex. Indeed, as with the somatotopic organisation of the motor cortex, the location of these phosphenes reflects the position of the coil relative to the retinotopic organisation of the primary visual area. However, studies of the primary visual cortex provided a second insight that has particular relevance for studies of cognitive function. Amassian and colleagues (summarised in Maccabee et al. 1991) found that stimuli too weak to evoke phosphenes were nevertheless capable of disrupting visual perception for a short period. They flashed three letters very briefly on to a computer screen and showed that recognition was disrupted if the occipital cortex was stimulated 80–130 ms after the letters were flashed. Given the timing of the effect, it appeared that the stimulus had interfered with processing of the signal coming into the primary visual cortex. Day et al. (1989) demonstrated a similar disruptive effect on motor cortex. They showed that TMS given after presentation of an imperative stimulus could increase reaction times by up to 150 ms, depending on the intensity of the stimulation. Unlike the situation in the visual cortex, the reaction was not abolished; it was delayed, indicating that the instructions for movement had been stored during the delay. The implication from both visual and motor studies was the same: a single TMS stimulus could not only activate cortex to produce an output that mimicked normal function, but that it could also disrupt any ongoing activity that was occurring at the time the TMS stimulus was given.

These experiments seemed to show that the disruptive effect of a single shock lasted 50–150 ms. However, a final important feature was noted by Amassian et al. (1993**)** in a variation of the letter-identification task. They showed that a 14-Hz train of three shocks, each of which was below threshold for producing any effect on visual perception when given alone, was capable of interfering with letter identification. In other words, disruption could be enhanced if short trains of stimuli were given.

The conclusion from these early experiments was that TMS could be used to disrupt cortical processing, and that this was particularly effective if short trains rather than single stimuli were given. This approach has proved particularly attractive in the study of cognitive function.

Mechanism of the disruptive effect of TMS

A single TMS stimulus to any area of cortex has two main effects. First, it produces synchronous activity in a subpopulation of neurones under the coil. The number of neurones involved depends on the intensity of the stimulus, but the net result is to disrupt any pattern of activity that was occurring at the time the stimulus was given. Second, synchronous activation of many cells causes release of a prolonged GABAergic IPSP that inhibits further activity for 50–250 ms (Fuhr et al. 1991; Ziemann et al. 1996**)**. In the motor cortex, this sequence of excitation followed by inhibition is seen as an initial muscle twitch followed by a period of silence in the EMG whilst the cortical activity is withdrawn. It is probably similar to the spike-wave electroencephalogram (EEG) activity of an epileptic focus: the spike represents initial excitation and the wave the later, longer inhibition. Depending on the number of neurones involved, this can lead to transient disruption of function for up to 250 ms.

The effects above are obviously most prominent in the cortex directly under the stimulating coil. However, effects at a distance also are well documented. For example, stimulation of the motor cortex of one hemisphere appears to inhibit activity in the homologous area of contralateral cortex (Ferbert et al. 1992; DiLazzarro et al. 1999). The inhibition lasts about 30 ms and can disrupt reflexes and volitional activity that pass through the cortex at that time. More recently, Paus et al. (1997) used positron emission tomography (PET) techniques to show that stimulation of frontal eye fields can cause activation

of occipito-parietal areas to which they are connected anatomically. However, whether this is excitatory or inhibitory cannot be determined from PET studies. The conclusion is that, although disruptive effects of TMS are most likely to come from cortex under the stimulating coil, effects from distant structures can also contribute to the disruption.

Initial applications of TMS involved delivery of single magnetic pulses with an approximate duration of 1 ms every few seconds. Since 1989, further technical advancement allows repetitive TMS using a train of pulses, which make it possible to disrupt brain function for a longer period of time and at higher frequencies. With some newer stimulators, it is possible to deliver stimulus trains lasting 10 s and to stimulate up to rates of 60 Hz. Given its growing popularity, it is worth considering the effect of short trains of TMS. The simplest scenario is that each stimulus will add to the next in a linear manner. Thus, two stimuli that alone disrupt activity for 100 ms might be expected to disrupt activity for 200 ms if they were applied one after the other with an interstimulus interval of 100 ms. To our knowledge this question has not yet been addressed directly, although the initial work of Amassian et al. (1993) suggests that, if anything, the effect of repeated stimuli may sometimes be more than the expected sum of each alone. In addition, data from experiments in which direct electrical stimulation was applied to the cortex in animals (Jankowska et al. 1975) suggests that the effect of trains of stimuli is likely to spread much further than a single shock, so that the spatial precision of any effect is reduced.

Following Churchland and Sejnowski (1988), it is useful to define the spatial and temporal resolution of any novel neuroscience technique so that we can characterise the particular range of phenomena that it is best suited to study. PET and functional magnetic resonance imaging (fMRI) have a spatial resolution in the mm range. Their temporal resolution is, in principle, limited by the time course of the haemodynamic response to metabolic load (of the order of a few seconds), but in practice is rather greater than this. In contrast, EEG and magnetoencephalography (MEG) have a spatial resolution of the order of half a cm for activity near the surface of the scalp, but this deteriorates quickly for deep sources. The temporal resolution is, however, excellent to ms ranges or less.

TMS has characteristics that fall between these values. As we have seen, the spatial resolution can be as good as half a cm for structures near the surface of the scalp, but, like EEG and MEG, falls off considerably for deep structures. The temporal resolution of the disruptive effect from a single shock is roughly of the order of 50–100 ms, but this is increased if trains are used. Thus, at the limit, we should be able to define very roughly when and where the cortex is active during a particular cognitive task within a distance of 0.5 cm on the scalp and to 50 ms in time.

A limitation of conventional TMS over other functional imaging techniques is that stimuli can only be given over one site at once; in contrast, EEG, MEG, PET and fMRI acquire data from the whole brain each time they are used. This means that, for example, mapping the brain is much more tedious with TMS than with other techniques. Indeed, if we wanted to map the location of a completely new brain activity for which there was no a priori information about the possible brain areas involved, TMS studies would take weeks or months, whereas this could be done in hours with other approaches. In practice, TMS studies are always informed by previous data on both the site and the time of stimulation. At first sight, this might seem to detract from the usefulness of the technique. However, this is not the case. TMS has one additional advantage over other human-brain imaging techniques: if TMS can disrupt task performance, then it has identified activity that is *essential* to, rather than just related to, task performance.

This reasoning leads to the following conclusion about the best design for experiments using the disruptive effect of TMS. First of all, areas of brain involved in a particular task are identified by other methods. TMS can then be used to tackle the following questions: (1) is this activity essential to task performance? (2) do different sites contribute to different aspects of the task? (3) are different sites essential at different times during the task? The studies discussed below illustrate all these approaches.

Effects of TMS on cognitive function

To illustrate the range of applications, a non-exhaustive list of the studies that have examined the effects of TMS over cortical sites other than the motor cortex is presented in Table 1. All of these studies have applied TMS over sites chosen on the basis of previous information from other brain-imaging or lesion studies.

Of the studies using TMS over *prefrontal* sites, some have been concerned with examination of higher-order aspects of motor function, such as response selection (Ammon and Gandevia 1990) and programming of periodic or generation of endogenous saccades (Beckers et al. 1992; Ro et al. 1997). Others have focused on investigation of disruptive effects of TMS on specific aspects of cognitive function, such as interference with free recall (Grafman et al. 1994), working memory (Pascual-Leone and Hallet 1994) or implicit learning (Pascual-Leone et al. 1994a, 1996b). Our own particular interest has been in applying TMS over the prefrontal cortex to examine the effects on the ability to suppress habitual or stereotyped responses during random-number- (Jahanshahi et al. 1998) or letter- (Jahanshahi and Dirnberger 1999) generation tasks. Repetitive TMS over the left frontal or parietal cortices has also been shown to interfere with linguistic processing, as evident from increased errors in a picture-word verification task, with retrieval of low-frequency words more affected than high-frequency words (Flitman et al. 1998). Stimulation over the supplementary motor area interferes with tim-

Table 1 Examples of investigations of the effects of transcranial magnetic stimulation over the prefrontal, premotor, parietal, temporal or occipital cortices

Brain area	Task	Authors
Prefrontal cortex	Hand selection in a two-choice reaction-time task	Ammon and Gandevia (1990)
	Programming of periodic saccades	Beckers et al. (1992)
	Working memory in a delayed-response task	Pascual-Leone and Hallett (1994)
	Free recall of verbal material	Grafman et al. (1994)
	Implicit learning during a serial reaction-time task	Pascual-Leone et al. (1996b)
	Controlled attention during visual search tasks with verbal or non-verbal stimuli	Sabatino et al. (1996)
	Generation of endogenous saccades	Ro et al. (1997)
	Random response generation	Jahanshahi et al. (1998); Jahanshahi and Dirnberger (1999)
	Linguistic processing in a picture-word verification task	Flitman et al. (1998)
SMA and premotor cortex	Performance of overlearned sequential finger movements	Amassian et al. (1991); Gerloff et al. (1997)
	Performance of sequences of memory-guided saccades	Muri et al. (1995, 1996)
	Response selection	Schulter et al. (1998)
Parietal cortex	Programming of periodic saccades	Beckers et al. (1992)
	Visual extinction of contralateral visual stimuli	Pascual-Leone et al. (1994b)
	Conjunction search	Ashbridge et al. (1997)
	Novel vs. learned serial conjunction search	Walsh et al. (1998)
Temporal cortex	Free recall of verbal material	Grafman et al. (1994)
	Arrest of speech with fronto-temporal TMS	Pascual-Leone et al. (1991); Jennum et al. (1994)
	Facilitation of picture naming	Topper et al. (1998)
Occipital cortex	Letter identification	Amassian et al. (1989)
	Colour perception	Maccabee et al. (1991)
	Identification of letter trigrams and memory scanning	Beckers and Homberg (1991)
	Programming of periodic saccades	Beckers et al. (1992)
	Visual motion perception	Beckers and Zeki (1995)
	Interhemispheric transfer	Marzi et al. (1998)

ing of sequential finger movements (Amassian et al. 1991; Gerloff et al. 1997) and with performance of sequences of memory-guided saccades (Muri et al. 1995), while TMS over the premotor cortex affects movement selection (Schulter et al. 1998).

TMS over the *parietal* cortex has been used to examine the programming of periodic saccades (Beckers et al. 1992), to induce visual extinction of contralateral visual stimuli when stimuli are simultaneously presented in both visual fields (Pascual-Leone et al. 1994b) and to influence conjunction search (Ashbridge et al. 1997; Walsh et al. 1998). Similar disruption of aspects of visual processing has been found with TMS over the *occipital* cortex, which has been shown to interfere with letter identification (Amassian et al. 1989; Beckers and Homberg 1991), colour perception (Maccabee et al. 1991), programming of periodic saccades (Beckers et al. 1992), visual motion perception (Beckers and Zeki 1995) and to reduce the rate of scanning in a Sternberg memory-scanning task (Beckers and Homberg 1991). Marzi et al. (1998) used TMS over the occipital cortex to examine interhemispheric transfer of visual information in a reaction-time (RT) task.

Interference with free recall of verbal material has been reported with TMS over *temporal* as well as frontal sites (Grafman et al. 1994); TMS over fronto-temporal sites has also been used to determine hemispheric dominance for language by producing speech arrest and has been shown to agree with the results of the intracarotid sodium amytal, or Wada test (Pascual-Leone et al. 1991; Jennum et al. 1994). In a number of studies, TMS has produced facilitatory effects on language-related processes. TMS over the Wernicke's area has been found to reduce the latency of picture naming (Topper et al. 1998) and to improve story recall (Pascual-Leone et al. 1993; Wassermann et al. 1996) at certain intensities.

Many of the studies above have been concerned primarily with identifying the site of disruption. TMS has also been used to identify the time window during which the contribution of an area is essential for performance (Muri et al. 1996) or the relative timing of the contribution of two or more areas to task performance (Beckers and Zeki 1995; Muri et al. 1996). This type of work can only be done when single, rather than trains of stimuli are used. For example, Muri et al. (1996) found that single pulses of TMS over the posterior parietal cortex and the dorsolateral prefrontal cortex, respectively, affected the percentage of errors in the amplitude of memory-guided saccades when applied 260 ms or in the time window 700–1500 ms after target presentation. The work of Amassian and colleagues (Amassian et al. 1993; Maccabee et al. 1991) and Beckers and Zeki (1995) has shown that TMS can identify the time course of transfer of information in the visual system, for example from striate to extra-striate cortices and from visual cortex to higher cortical areas such as the inferior temporal lobe.

A further application of TMS has been to investigate changes in excitability of cortical target areas during learning. Using motor-cortical mapping with TMS, Pascual-Leone et al. (1994a) demonstrated that implicit learning during a serial reaction-time task was associated with progressive expansion of the cortical output maps of the muscles involved in the task until explicit knowledge of the repeating sequence was developed, at which point the maps returned to their baseline topography. This illustrated the rapid plasticity of cortical output in the course of learning. In a subsequent study, Pascual-Leone et al. (1996b) showed that TMS over the dorsolateral prefrontal cortex blocked implicit learning on a serial reaction-time task, whereas TMS over the supplementary motor area did not interfere with learning. Walsh et al. (1998) examined the effect of TMS over the right parietal cortex during a visual search task before and after perceptual training on the task. Following extensive training, the initially disruptive effect of TMS on performance disappeared, but was reinstated when subjects were tested on a new visual search array. These studies indicate that TMS is a useful tool for investigating cortical plasticity and the changes that occur in function with learning. As discussed below, it may be possible to exploit TMS to investigate other forms of reorganisation of cognitive function that occur, for example following disease or injury or after medication, surgical intervention or rehabilitation therapy.

It is probably fair to say that most of these early studies have used TMS only to confirm previous ideas about the role of various cortical areas in different tasks. However, as the technique becomes more firmly established, more interesting experimental designs are appearing. For example, Sadato et al. (1996) performed a PET study on Braille reading in early blind subjects. They found activation of primary visual cortex as well as somatosensory cortex, whereas sighted subjects reading embossed Roman letters only activated conventional sensory areas. TMS was then used to tackle the question of whether the primary visual activity in the blind was contributing to task performance or whether the increased blood flow there was an epiphenomenon unrelated to the task (Cohen et al. 1997). Trains of TMS were shown to disrupt performance of blind Braille readers, but not normal-sighted subjects, suggesting very strongly that there had been a functional reorganisation of somatosensory processing in the blind individuals.

Procedural considerations: design of experiments using TMS

Although TMS is often said to be a painless way of stimulating the brain through the scalp, it is not devoid of sensation. First, discharge of the stimulator through the coil produces a loud click that is very difficult to conceal even with headphones playing white noise. Second, there is a definite tactile sensation on the scalp that may be due to stimulation of large-diameter cutaneous afferents under the coil. Depending on the site of stimulation, this is accompanied by a muscle twitch caused by stimulation of motor nerves to scalp muscle. The latter effect is minimal for stimulation of midline sites near the vertex, since no muscle is attached in that area. However, there are large masses of muscle near frontal, temporal and occipital areas, and the sensation produced by stimulation at these sites can sometimes be quite strong or even unpleasant (particularly with trains of stimuli). At the most lateral scalp sites, stimulation will also activate facial and trigeminal nerves; stimulation over prefrontal areas may activate the supraorbital nerve. Stimulation at virtually any scalp site will produce a blink reflex, although whether this produces an overt movement of the eyelids depends on the site and intensity of stimulation.

All of these sensory inputs may potentially interfere with performance of cognitive tasks, so that a first principle of experimental design must be to exclude these phenomena and prove that disruptive effects are due to interference with brain function, not to sensory input. Two designs can control for these sensory effects. In a *"control site"* design, the effects of TMS at a target and a control site are compared, with TMS predicted to produce an effect over the target, but not the control site. An example of this type of design is found in the studies of effects of TMS on random-response generation by Jahanshahi et al. (1998) and Jahanshahi and Dirnberger (1999), which compared the effect of TMS over the left prefrontal cortex with TMS over the right and medial frontal cortices. In both studies, only TMS over the left prefrontal cortex produced significant and specific changes in random response generation. In the *"control task"* design, the effects of TMS on experimental and control tasks are compared, with TMS predicted to produce an effect on the target task incorporating the process(es) of interest, but not on the control task. An example of this design is the study of Flitman et al. (1998), who found that TMS over a left anterior site affected the accuracy of a picture-word verification but, not a frame verification task. Of course, it is possible to incorporate either of these designs in a single study. For example, Flitman et al. (1998) combined a control task and a control site design. A *"control time"* design is sometimes useful. Here, the effects of TMS at several points in time during task performance are compared, with TMS predicted to produce an effect at particular times in the course of task performance and not at other times. An example of this design is found in the work of Beckers and Zeki (1995) and Muri et al. (1996). Beckers and Zeki (1995) found that TMS over V5 when delivered at intervals of –20 to +10 ms before or after the onset of visual stimulation abolished motion perception. However, since sensory input at particular times could potentially have the same effect, a "control time" design is not adequate unless combined with one of the other two designs. Of course, it is possible to incorporate any two or all three of these designs in a single study. For example, Flitman et al. (1998) combined a "control task" and a "control site" design, while the study by Beckers and

Zeki (1995) can be considered to employ a "control site" and "control time" design.

Compared with studies of the motor cortex, it is much more difficult to measure the effects of TMS on cognitive function. Commonly, this involves measuring the latency (Ammon and Gandevia 1990; Pascual-Leone et al. 1996b; Wassermann et al. 1999) or accuracy of responses (Pascual-Leone and Hallett 1994; Gerloff et al. 1997; Wassermann et al. 1999), or the introduction (Ammon and Gandevia 1990; Amassian et al. 1991) or alteration of some specific response bias (Jahanshahi et al. 1998; Jahanshahi and Dirnberger 1999). Interruption of ongoing behaviour, such as speech arrest (Pascual-Leone et al. 1991; Jennum et al. 1994), has also been used as an outcome measure. However, because of differences in the variance of the response measure, a reliable estimate of the size of an EMG response from motor stimulation can be achieved with only 10–20 stimuli, whereas reliable estimates of changes in reaction time or response bias may require 50–100 or more trials. Since the latter also involve much greater attentional resources of the subject, it may be difficult, for example, to repeat sufficient trials to map the scalp location of the effect in the same detail as for the motor areas.

Several other procedural considerations such as the size and shape of the stimulating coil, localisation of the site of stimulation, choice of suitable control sites, the intensity of stimulation and the number of trials needed to obtain a reliable effect are common to all TMS studies regardless of site of stimulation. For repetitive TMS, it is also necessary to decide the number of pulses in a train and the intervals between them. Since repetitive TMS does carry a serious risk of epileptic seizures and seven such TMS-induced seizures have been documented between 1989 and 1996 (Wassermann 1998), careful screening of subjects and adherence to safety guidelines (Pascual-Leone et al. 1993; Jahanshahi et al. 1997b; Wassermann 1998) is crucially important.

Future applications

There is now a budding literature on the application of TMS to the study of cognition or higher-order aspects of motor control. Undoubtedly, we will witness many such original applications in future studies. Several considerations may prove particularly fruitful in such future applications. First, the main focus of the existing TMS studies of cognition has been on examining the effects produced by stimulation over specific target sites. The temporal specificity of the technique has so far been less-widely exploited. TMS has the potential of revealing the time course of specific processes during task performance or the time at which involvement of a specific cortical area is crucial. Second, the development of suitable control tasks that either do or do not share a process of interest with the experimental task may allow the nature of the processes that are disrupted by TMS to be discerned. A third possibility that has already been exploited to some extent is the adoption of a multi-technique approach to the study of a facet of cognitive function. Our own studies of random-response generation demonstrate the utility of adopting such a multi-technique, albeit non-concurrent, approach to the study of generation of random responses. The converging sources of evidence from PET (Jahanshahi et al. 1997a), TMS (Jahanshahi and Dirnberger 1999; Jahanshahi et al. 1998) and clinical studies in Parkinson's disease and experimental studies using dual-task methodology (Brown et al. 1998) have revealed not only the functional anatomy of random-response generation, but also the role played by the dorsolateral prefrontal cortex in generation of such responses. Other investigators have successfully combined TMS concurrently with other techniques. The EEG has been recorded in combination with TMS to explore transcallosal (Cracco et al. 1989) or cerebello-frontal (Amassian et al. 1992a) patterns of connectivity in the human brain. More recently, Paus and colleagues (1997) successfully combined the concurrent use of TMS with PET and found a significant correlation between cerebral blood flow and the number of TMS pulse trains at the stimulation site over the frontal eye fields (FEF) and, more distally, in the visual cortex in the superior parietal and parieto-occipital areas. These results highlight the potential value of the combined techniques for exploring functional and anatomical connectivity in the intact human brain in normal subjects and patients with neurological or psychiatric disorder.

There is now evidence that the ventral dentate nucleus projects to the dorsolateral prefrontal cortex (Middleton and Strick 1994) and that the cerebellum may be involved in aspects of cognitive function (Leiner et al. 1995). TMS over the cerebellum, which has been used to transiently suppress motor cortex excitability (Ugawa et al. 1991), could prove valuable for exploring the specific role of the cerebellum in cognitive function. For example, paced random-number generation involves suppression of habitual responses and response selection and is a task that engages working memory. The task has been shown with PET to activate both the dorsolateral prefrontal cortex and several foci in the cerebellum compared with a control counting task (Jahanshahi et al. 1997a). These foci included the dentate nucleus, which showed rate-dependent change and was possibly related to the pacing demands of the task, and the right and left cerebellar hemispheres, which probably reflected articulatory rehearsal of responses to maintain an "on-line" record of the last few responses (Jahanshahi et al. 1997a). TMS over the cerebellum during random-number generation may clarify the functional significance of the activations observed with PET.

Table 2 presents a number of other possible applications of TMS in the study of cognitive function that have not as yet been exploited. With motor responses, it has been shown that TMS can also provide information about patterns of connectivity between various brain regions, such as the cortico-cortical (Kujirai et al. 1993), transcallosal (Cracco et al. 1989; Ferbert et al. 1992) or cerebel-

Table 2 Examples of questions that may be possible to address with transcranial magnetic stimulation in studies of cognitive function

Temporary lesion effect	Whether the contribution of a target area is *essential* for performance
Timing of involvement of a target area	The time window during which the contribution of an area is essential for performance
Relative timing	The relative timing of the contribution of two or more areas to task performance
Plasticity with learning	What changes in excitability occur in target areas with learning
Intracortical and transcallosal connectivity	What effect does subthreshold stimulation of one area have on subsequent suprathreshold stimulation of another target site
Effects of medication	What changes in excitability occur in target areas with medication and the time course of these changes
Effect of surgical or rehabilitative interventions	What changes in excitability occur in target areas following interventions such as surgery or cognitive rehabilitation programmes
Effect of brain damage/disease	What changes in excitability occur in target areas following brain damage, neurological or psychiatric illness

lo-frontal regions (Amassian et al. 1992a). With appropriate means of quantifying the effects, it may also be possible to use the double-pulse TMS technique, which examines the effect of a subthreshold conditioning TMS pulse over one site on the size of a response evoked by a suprathreshold test TMS pulse over a second site to examine cortico-cortico, transcallosal and cerebello-frontal patterns of connectivity during performance of cognitive tasks. Alternatively, using TMS in conjunction with functional imaging or high-resolution EEG may provide information about patterns of brain connectivity during cognitive tasks. The various functional systems of the brain do not work in isolation, but interact. TMS can be used to investigate such functional interactions. For example, Tokimura et al. (1996) showed that for right-handed subjects, while spontaneous speech increased the size of EMG responses bilaterally, reading aloud increased EMG responses in the right hand only. This suggests that reading aloud increases the excitability of the motor hand area in the dominant hemisphere, suggesting functional interaction between the speech and motor-output functions of the dominant hemisphere. Such functional interactions during cognition could be explored with TMS.

TMS has been used to investigate the effect of various pharmacological agents on motor-cortex excitability (e.g. Ziemann et al. 1996). In a similar fashion, examining the effects of TMS on target cortical sites such as the prefrontal or temporal cortices before and after administration of particular types of medication may clarify the modulatory impact of pharmacologic agents, such as dopaminergic or cholingergic agonists or antagonists on cognitive processes of interest. TMS has also been widely used as a clinical research tool to examine the effect of neurological illnesses such as Parkinson's disease (Ridding et al. 1995) or brain injury following stroke (e.g. Turton et al. 1996) on motor function. It should be possible to employ TMS to study the impact of neurologic or psychiatric illness or brain injury on various aspects of cognitive function and changes that may occur in these over time with progression of the illness or following surgery or rehabilitation. For instance, it is now recognised that, in the first six months after a stroke, major recovery of function, including motor function, speech and other aspects of language, can occur. PET has shown that movements with the recovered arm are associated with *bilateral* increases of regional cerebral blood flow in premotor areas, parietal and prefrontal cortices (Chollet et al. 1991). The bilateral activation suggests that recruitment of ipsilateral pathways may play a role in recovery of function following stroke. However, using TMS, Turton et al. (1996) have demonstrated that ipsilateral responses from the undamaged hemisphere were more prevalent in poorly recovered patients, suggesting that this may not be beneficial for recovery of function. TMS may be equally valuable for determining whether the restitution of activation patterns in networks involved in language processing that are associated with recovery of aphasia after stroke signify that the relevant areas have returned to normal functioning or not.

There is evidence that TMS produces facilitatory effects on certain aspects of function. Faster speed of responding and improved recall of verbal material have been documented following repetitive TMS (Pascual-Leone et al. 1993). In Parkinson's disease, subthreshold repetitive TMS has been shown to significantly shorten reaction times and movement times (Pascual-Leone et al. 1994c). It may be possible to exploit such facilitatory effects as part of cognitive rehabilitation programmes, in the same way that repetitive TMS over the left dorsolateral prefrontal cortex has been applied to treat chronic depression (George et al. 1995; Pascual-Leone et al. 1996a), and 1-Hz stimulation has been employed to treat post-traumatic stress disorder (McCann et al. 1998). Repetitive TMS may prove beneficial in altering speed of processing or accessibility and retrieval of memories.

In its relatively short life span, TMS has evolved from reliance on single pulses to repetitive stimulation and design of coils that allow more focal stimulation. Future re-

finements of TMS are bound to improve its spatial and temporal specificity and render it a unique technique for the investigation of cognitive function in man. Hopefully, in the interim, a clearer understanding of the precise mechanisms of action of TMS over sites other than the motor cortex will also be obtained.

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