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Transcranial magnetic stimulation: studying the brain–behaviour relationship by induction of 'virtual lesions'

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Transcranial magnetic stimulation (TMS) provides a non-invasive method of induction of a focal current in the brain and transient modulation of the function of the targeted cortex. Despite limited understanding about focality and mechanisms of action, TMS provides a unique opportunity of studying brain–behaviour relations in normal humans. TMS can enhance the results of other neuroimaging techniques by establishing the causal link between brain activity and task performance, and by exploring functional brain connectivity.

Keywords: transcranial magnetic stimulation; brain–behaviour relation; non-invasive

Transcranial magnetic stimulation (TMS) allows the safe, non-invasive and relatively painless stimulation of the brain cortex if appropriate guidelines are followed (Wassermann 1998). Therefore, unlike other techniques of cortical stimulation, TMS can be used in the study of normal subjects and patients with a variety of neuropsychiatric conditions rather than being restricted to patients undergoing neurosurgical procedures for medically intractable epilepsy or focal brain lesions. TMS can be used to complement other neuroscience methods in the study of central motor pathways (Rossini & Rossi 1998), the evaluation of corticocortical excitability (Rothwell 1997; Pascual-Leone *et al*. 1998) and the mapping of cortical brain functions (Hallett 1996). In addition, TMS provides a unique methodology for determining the true functional significance of the results of neuroimaging studies and the causal relationship between focal brain activity and behaviour.

Traditionally, 'lesion studies' have represented the best way of establishing a causal link between brain function and behaviour. Nowadays, neuroimaging techniques allow identification of the brain injury correlated with a given behaviour non-invasively. Not only is it possible to delineate the lesion of a patient carefully, but it is also possible to reconstruct *a posteriori* the lesion of patients based on partial data from brain and skull anatomy and the known information about mechanism of injury. However, this lesion study approach is probably hampered by the plastic capabilities of the brain. Following a brain injury, brain function reorganizes in an attempt to compensate for the lost abilities and, therefore, the observations might yield inaccurate results. Furthermore, cognitive abilities might be globally impaired after a brain insult so that the patient might not be suited for extensive, detailed testing of a given ability. Patients will frequently have more than a single brain injury or the brain injury might be larger than the brain area under study making the correlation between regional brain function and disturbed behaviour difficult. Finally, lesion studies depend on the opportunity and chance occurrence of a given brain injury and, thus, cannot be planned in advanced or designed with care, are generally limited to a single or few case studies and cannot be repeatedly tested for confirmation.

Applied as single pulses appropriately delivered in time and space or in trains of repetitive stimuli at appropriate frequency and intensity, TMS can be used to disrupt the function of a given cortical target transiently, thus creating a temporary 'virtual brain lesion'. This allows the study of the contribution of a given cortical region to a specific behaviour. This technique has multiple advantages over lesion studies. First, TMS studies can be conducted in normal subjects, thus eliminating the confounds of additional brain lesions. Second, TMS studies can be conducted acutely, avoiding the possibility of plastic reorganization of brain function. Third, TMS studies can be repeated in the same subject, providing an opportunity for careful, controlled experimental design. Fourth, multiple subjects can be tested with the same experimental paradigm, thus allowing statistical evaluation of the results. Fifth, different, neighbouring brain structures can be targeted in each subject thus allowing precise mapping of the behaviour disruption to a given brain area. Sixth, different related behavioural tasks can be tested, thus allowing the identification of the specific contribution of a cortical area to a cognitive function and ruling out more global mental impairment. Therefore, TMS provides a novel approach to the scientific study of regional brain function and behaviour by the possibility of 'creating' virtual patients.

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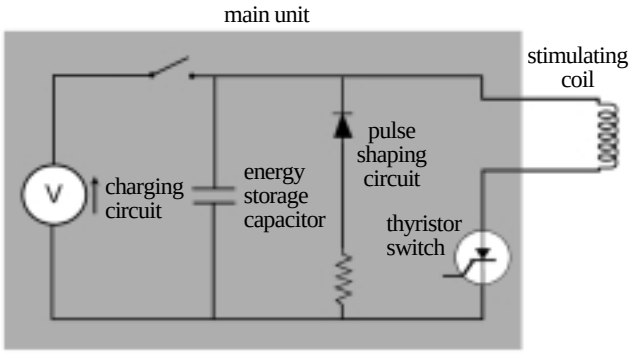

Figure 1. Simplified schematic diagram of a standard (single-pulse) magnetic stimulator. Modified from Barker (1991).

Nevertheless, it appears that the concept of localization of brain function to a specific brain area is incorrect. The primate brain seems to be a mosaic of highly interconnected, spatially distributed and distinct regions. Lesions of these corticocortical and corticosubcortical connections result in specific neurological and psychiatric 'dysconnection' syndromes. Therefore, human brain function and behaviour seems best explained on the basis of functional connectivity between brain structures rather than on the basis of localization of a given function to a specific brain structure. This approach of explaining normal behaviour and neuropsychiatric disorders at the level of distributed neural networks requires a technique for identification of corticocortical and corticosubcortical functional connectivity *in vivo*. It is not sufficient to know that anatomical connections exist between two different brain areas. The critical question is whether such connections and, thus, the correlated function of the two brain areas are required for a given behaviour. Functional neuroimaging techniques such as positron emission tomography (PET) have convincingly shown the association between certain behaviours and specific patterns of joint activation of cortical and subcortical structures. Functional magnetic resonance imaging (fMRI) studies can add greater anatomical resolution and the temporal profile of the pattern of activation of such neural networks for specific behaviours. However, in the best of circumstances, these neuroimaging techniques only provide supportive evidence of the neural network associated with a given behaviour rather than direct, causal evidence. Activation of a given neural network by a behaviour can establish an association between neural activity and behavioural manifestation, but does not provide insight into the role that a given neural structure or its connections play in the behavioural manifestation. In addition, different strategies in behaviour are difficult to control for and might induce misleading results in such 'associative' approaches of correlation between behaviour and brain activity.

The combination of TMS and functional neuroimaging techniques provides a novel approach to solving this problem (Paus 1999). First, activity in different brain areas identified by fMRI or PET to be associated with a given behaviour can be systematically disrupted by TMS in order to assess their causal role in the behavioural manifestation (Cohen *et al*. 1997). In this case, fMRI or PET would provide a guide to TMS applied to create virtual patients as discussed above. Second, TMS can be applied to a given cortical area and its activity can be modulated, increased or decreased transiently, while the subject performs a given behaviour and the brain activity associated with such behavioural activation is measured using fMRI or PET. In this case, fMRI and PET studies could evaluate the functional adaptation of brain activity to the modulation of neural activity in an element of a neural network whose activity has been previously demonstrated to be associated with a given behaviour (Pascual-Leone *et al*. 1998). Finally, instead of using a cognitive task, TMS can provide a controlled stimulation of a specific region of the subject's brain (Fox *et al*. 1997; Ilmoniemi *et al*. 1997; Paus *et al*. 1997; Bohning *et al*. 1999). In this case, concurrent measures of regional blood-flow or EEG during and following TMS could be used to assess functional brain connectivity independently of the subject's behavioural state. Therefore, the interindividual variability in task strategy could be eliminated. These different approaches promise to enhance the potential of functional neuroimaging techniques by allowing the establishment of causal links between brain activity and behaviour and the behaviour-independent assessment of functional neural connections in the living brain.

The principles that underlie TMS were discovered by Michael Faraday in 1831 (Faraday 1965). A pulse of current flowing through a coil of wire generates a magnetic field. The rate of change of this magnetic field determines the induction of a secondary current in any nearby conductor. In TMS, the stimulating coil is held over a subject's head and, as a brief pulse of current is passed through it, a magnetic field is generated that passes through the subject's scalp and skull without attenuation (only decaying by the square of the distance). This time-varying magnetic field induces a current in the subject's brain. Therefore, strictly speaking, transcranial magnetic stimulation is a misnomer, as the magnetic field appears to simply represent a bridge between the current in the stimulating coil (primary current) and the current induced in the subject's brain (secondary current). In TMS, neural elements are not primarily affected by exposure to a magnetic field but, rather, by the induced secondary current. Therefore, TMS might be best considered a form of 'electrodeless, non-invasive electric stimulation'. Nevertheless, the electromagnetic induction of the secondary current does result in critical differences between the effects of TMS and those of direct or transcranial electric stimulation (Rothwell 1997).

In the early 1980s, Barker *et al*. (1985) developed the first compact magnetic coil stimulator at the University of Sheffield. Soon after, TMS devices became commercially available. These original 'single-pulse' magnetic stimulators were limited to stimulation rates of 0.3–0.5 Hz. The development of 'rapid' or 'high-frequency' magnetic stimulators that allow TMS at rates of up to 60 Hz has greatly expanded the potential applications of this technique (Pascual-Leone *et al*. 1997).

The design of magnetic stimulators is relatively simple (Barker 1991; Cadwell 1991; Jalinous 1991). They consist of a main unit and a stimulating coil (figure 1). The main unit is composed of a charging system, one or more energy storage capacitors, a discharge switch, and circuits for pulse shaping, energy recovery and control functions. Different charging systems are possible; the simplest

design uses step-up transformers operating at a line frequency of 50–60 Hz. The critical design requirements for charging systems are charging speed and accuracy in order to allow repetitive TMS (rTMS) and ensure that all stimuli in a train are of equal amplitude. Energy storage capacitors can also be of different types and the amount of stored energy required depends on the circuit type and the waveform of the magnetic field generated (monophasic, biphasic or polyphasic). The essential factors in the effectiveness of a magnetic stimulator are the speed of the magnetic field rise time and the maximization of the peak coil energy. Therefore, large-energy storage capacitors and very efficient energy transfer from the capacitor to the coil are important. Typically, energy storage capacity is *ca*. 2000 joules, and 500 joules are transferred from the capacitors into the stimulating coil in less than 100 μs. Storage capacitors are discharged into the stimulating coil via a thyristor, an electronic device that is capable of switching large currents in a few microseconds. The peak discharge current needs to be several thousand amperes in order to induce currents in the brain of sufficient magnitude to depolarize neural elements (approximately 10 mA cm^{-2}). After flowing through the stimulating coil the current is returned to the capacitors using an energy recovery circuit, thus speeding up the charging time and minimizing coil heating. Thyristors, diodes and passive components are used to shape the discharge waveform (pulse shaping circuit). The cost, complexity of design, reliability, stimulation accuracy, stimulating coil heating, discharge click noise and discharge repetition rate are some of the factors that condition the choice of the discharge waveform, generally a fixed characteristic of each magnetic stimulator. A monophasic device is slower but more accurate, allowing for more detailed studies of the mechanisms involved in TMS of nerves or the brain (Brasil-Neto *et al*. 1992*a*). Monophasic devices can be easily paralleled, thus allowing the discharge of two or more devices simultaneously for higher output power and the delivery of two stimuli with very short interstimulus intervals (paired-pulse TMS) (Kujirai *et al*. 1993). On the other hand, biphasic devices are faster and, thus, allow higher repetition rates of stimulation (rTMS). Polyphasic devices are rarely used as they are associated with the loudest discharge click noise, produce the most heat in the stimulating coil, and their discharge energy cannot be recovered after each stimulus, thus limiting the repetition rates of rTMS.

During transcranial brain stimulation only the stimulating coil needs to come in close contact with the subject. Stimulating coils consist of one or more well-insulated coils of copper wire frequently housed in a moulded plastic cover. Copper is used for construction of stimulating coils due to its low electrical resistance, high heat capacity, good tensile strength and ready availability. During the discharge of a magnetic pulse the stimulating coil is subjected to high voltages and substantial forces which depend on coil size, geometry and peak energy. Therefore, careful construction is essential. Stimulating coils are available in a variety of shapes and sizes (Cohen *et al*. 1990). Larger circular coils use more copper mass, thus having lower electrical resistance and higher heat capacity. Figure-of-eight coils (also called butterfly or double coils) are constructed with two windings placed

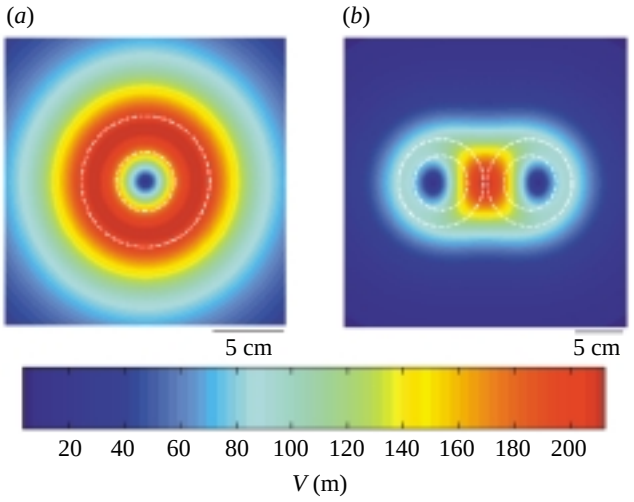

Figure 2. Distribution of the induced electric fields by (*a*) a circular and (*b*) a figure-of-eight stimulating coil. The circular coil has 41.5 mm inside turn diameter, 91.5 mm outside turn diameter, 66.5 mm mean diameter and 15 turns of copper wire. The figure-of-eight coil has 56 mm inside turn diameter, 90 mm outside turn diameter, 73 mm mean diameter and nine turns of copper wire per winding. The outline of both coils is depicted with dashed white lines on the representation of the induced electric fields. The electric field amplitude is calculated in a plane 20 mm below a realistic model of the coil ($dI/dt = 10^8$ A s^{-1}). Modified from figures created by Anthony Barker for the Harvard Course on Transcranial Magnetic Stimulation (December 1997).

side by side and provide the most focal means of brain stimulation with TMS available to date (Ueno *et al*. 1988; Maccabee *et al*. 1990; Cohen & Cuffin 1991; Yunokuchi & Cohen 1991; Ruohonen *et al*. 1997). Four-leaf magnetic coils (Roth *et al*. 1994) and other, more complicated geometries and newer construction materials might in the future provide more focal stimulation coils. In the case of a circular coil the induced tissue current is maximal under the mean diameter and is near zero in the centre of the coil (figure 2) (Cohen *et al*. 1990; Maccabee *et al*. 1990; Tofts 1990; Roth *et al*. 1991). In the case of the figure-of-eight coil practically only neural structures under its centre (at the intersection of the two wings of the coil) are stimulated (figure 2) (Cohen *et al*. 1990; Maccabee *et al*. 1990; Tofts 1990; Roth *et al*. 1991).

Precise determination of the focality of TMS is important in the accurate interpretation of experimental results and the design of experimental paradigms. However, much work is still required to resolve this issue fully. The figure-of-eight stimulating coil is generally used in studies aiming for focal brain stimulation. Nevertheless, it is important to remember that, at high stimulation intensities (over twice the stimulation threshold), smaller peripheral peaks of the magnetic field generated (approximately half the amplitude of the central peak) on either side of the figure-of-eight coil may also cause brain stimulation. Furthermore, knowledge of the magnetic field (for example, from mathematical models or measurements) does not really help in the determination of the actual induced electrical field and, thus, the focality of TMS in the brain. Empirical MRI phase maps of TMS perturbations (Bohning *et al*. 1997) simply

confirm the lack of attenuation of the magnetic field by skin and bone and do not provide insight into the site or focality of brain stimulation. The amplitude of the induced electric field is a function of the distance between the coil and the tissue, the stimulator output and the coil construction, geometry and orientation (Epstein *et al*. 1990). In addition, the current density induced by TMS in the brain will vary with local tissue impedance. Therefore, actual measurements of TMS-induced voltages or currents in the brain of humans or animal models are needed. Lissanby *et al*. (1998) have begun to conduct such experiments in monkeys. In humans, measurements in cadavers or in patients being evaluated for epilepsy surgery with implanted depth electrodes would yield invaluable information. However, the safety of TMS in patients with implanted brain electrodes needs to be properly tested and established.

The problem of the focality of TMS becomes even more complex when considering the fact that neural structures will vary in their threshold ('vulnerability') to TMS depending on their orientation in the tissue and the presence or absence of sudden bents (Maccabee *et al*. 1993). Therefore, rather than assuming that TMS focuses its effects on a discrete brain spot, we might be better served by considering that it affects a blurred volume of brain tissue and within it different structures depending on orientation and fibre paths. Nevertheless, this limitation does not extend to the degree that one cannot claim preferential effects on a given brain structure or rule out direct extension of the TMS effects to distant cortical areas. It is probable that the effects of TMS (particularly of rTMS) might spread along neural connections to affect distant cortical and subcortical structures (Fox *et al*. 1997; Ilmoniemi *et al*. 1997; Paus *et al*. 1997; Pascual-Leone *et al*. 1998; Bohning *et al*. 1999). Nevertheless, direct TMS effects to a given cortical target appear to be limited to a definable tissue volume. The size of this tissue volume directly affected by TMS might in turn be different for single-pulse TMS and repetitive TMS due to intracortical spread of excitation (Pascual-Leone *et al*. 1994*c*), a phenomenon dependent on stimulation intensity, frequency and duration. In this sense TMS focality might be thought of in a similar manner as the thresholded findings of functional neuroimaging techniques. Specific 'hot spots' for a given function are affected by TMS to specific cortical targets.

Some empirical studies of TMS applications support this notion of focality of the TMS effects. Mapping studies of the cortical motor outputs generated by TMS applied with a small figure-of-eight coil to successive neighbouring scalp positions suggest a spatial resolution of approximately 0.5–1 cm (Brasil-Neto *et al*. 1992*b*; Wilson *et al*. 1993). However, this degree of focality is probably in part misleading (Thickbroom *et al*. 1998). The extent of the TMS motor output maps seems largely determined by current spread and by the relationship between the position of the coil on the scalp and the depth of the motor output region in the cortex (Thickbroom *et al*. 1998). Studies correlating the findings of TMS motor output maps and PET (Wassermann *et al*. 1996), fMRI (Krings *et al*. 1997*a*; Bastings *et al*. 1998; Terao *et al*. 1998*b*) or direct cortical stimulation experiments (Cohen *et al*. 1989; Krings *et al*. 1997*b*) have provided critical information. They suggest that TMS is comparable to these other brain mapping methods in terms of focality, spatial resolution and specificity of the effects.

A problem related to the question of the focality of TMS is the anatomical correlation of the effects. TMS is applied with the coil held over a specific site on the subject's scalp with the intent of targeting a specific brain cortical area. However, brain–scalp relationships are quite variable across individuals so that placement of the TMS coil on the scalp according to bony landmarks will necessarily introduce errors and interindividual variability in the targeted brain region (Meyer *et al*. 1991). This variability might be reduced by referring a given coil position on the scalp to the optimal scalp position for activation of contralateral intrinsic hand muscles as determined by TMS motor mapping (Wassermann *et al*. 1992). This 'optimal scalp position' has been shown to correspond reliably to the location of the central sulcus and the primary motor cortex (Wassermann *et al*. 1996). However, even so, there is substantial error introduced due to variability in brain size and anatomy. For example, studies on the antidepressant effects of TMS in depression (Pascual-Leone *et al*. 1996*a*; George *et al*. 1997) have generally targeted the dorsolateral prefrontal cortex as defined by the position of the TMS coil on the scalp 5 cm anterior and in the same parasagittal plane as the optimal scalp position for activation of the contralateral abductor pollicis brevis muscle. Figure 3 illustrates the substantial variability in the brain structure actually targeted by TMS when this method is employed. Obviously, assuming focal specificity of the effects of TMS, such variability may well condition large interindividual differences in study results.

Head surface digitization and registration of the TMS stimulation sites onto the subject's three-dimensional reconstructed head MRI can help address the issue of anatomical specificity of the TMS effects by identifying the actual brain target in each experimental subject (Wang *et al*. 1994; Wassermann *et al*. 1996; Miranda *et al*. 1997; Bastings *et al*. 1998). The use of optical digitization and frameless stereotactic systems represents a further improvement by providing on-line information about the brain area targeted by a given coil position on the scalp. The head MRI of the subject is obtained ahead of the TMS study and displayed on a workstation that integrates it with the subject's head and coil position in real time (Krings *et al*. 1998; Paus & Wolforth 1998; Potts *et al*. 1998). In addition, with such systems it is possible to monitor all degrees of freedom of the coil, thus assuring a constant position and angle of the coil on the scalp and, therefore, a constant brain target. Commercially available frameless stereotactic systems have been developed for neurosurgical procedures, but they are very expensive and include a list of features not actually required for TMS work. Eventually, the development of similar systems for specific use in TMS studies will be desirable.

The use of such frameless stereotactic systems provides the additional advantage that fMRI (rather than anatomical MRI) images can be used to guide the site of TMS. In doing so, both the focality and site specificity of TMS as well as the true functional significance of an area of activation on fMRI can be addressed. Figure 4 illustrates such an approach in a study on visual area V5 and

motion detection. A BOLD-contrast fMRI demonstrates the areas of activation associated with random and vection motion allowing the identification of the presumed area V5. TMS was applied to a series of scalp positions 1.5 cm × 1.5 cm apart around the scalp site overlaying the fMRI-identified area V5. TMS led to a significant impairment in the detection of motion direction only from the single scalp position overlying the cortical area of activation on fMRI.

In addition to the critical problem of focality of TMS and anatomical correlation of the effects, the mechanisms underlying the cortical effects of TMS remain filled with questions and unknowns. Currents induced in the brain by TMS flow parallel to the plane of the stimulation coil (approximately parallel to the brain's cortical surface when the stimulation coil is held tangentially to the scalp). Therefore, in contrast to direct or transcranial electrical cortical stimulation, TMS preferentially activates neural elements orientated horizontally to the brain surface. Exactly what neural elements are activated by TMS remain unclear and may in fact be variable across different brain areas and different subjects. Applied to the motor cortex, TMS appears more probable to produce indirect than direct waves in the descending corticospinal volley (Day *et al.* 1987; Amassian *et al.* 1989; Edgley *et al.* 1990; Nakamura *et al.* 1996; Sakai *et al.* 1997; Di Lazzaro *et al.* 1998*a*; Houlden *et al.* 1999). This suggests preferential trans-synaptic activation of pyramidal neurons and a direct effect of TMS on cortical interneurons. However, this seems largely restricted to relatively low TMS stimulation intensities and certain TMS coil orientations (Kaneko *et al.* 1996*a*; Sakai *et al.* 1997; Houlden *et al.* 1999). Certainly much more work is needed in order to refine our understanding of the mechanisms of action of TMS in the brain cortex. Studies in animals would be desirable and indeed raise questions about the neural elements primarily affected by TMS (Edgley *et al.* 1990; Baker *et al.* 1994). Unfortunately, animal studies of TMS face some methodological limitations (Weissman *et al.* 1992). The peak voltage induced by TMS in the brain is inversely proportional to the head radius, and the stimulation efficiency depends on the ratio between the head and coil size. If the head is smaller than the stimulating coil, less magnetic flux is captured, thus decreasing the efficiency of the stimulation (Weissman *et al.* 1992). Therefore, studies on the effects of TMS performed in rodents employing human-sized coils are of limited meaning. Specially constructed small coils that reproduce the human coil : head size ratio will overcome this limitation. However, such small coils are prone to overheating at the stimulation levels commonly used in humans.

TMS studies in neurosurgical patients provide a unique opportunity for detailed neurophysiological studies and promise to critically advance our understanding about the mechanisms of action of TMS. Much of our current understanding about the mechanisms of the corticospinal motor effects of TMS is derived from studies in patients undergoing spinal cord surgery and monitored with epidural or subdural spinal electrodes. Such studies allow precise determination of the components of the TMS-induced descending pyramidal volley in a variety of different application modes and conditions (Kaneko *et al.* 1996*a*,*b*; Nakamura *et al.* 1996, 1997; Di Lazzaro *et al.* 1998*a*,*b*,*c*; Houlden *et al.* 1999). Similar studies in patients with implanted depth electrodes might provide unique insights into the corticocortical and corticosubcortical interactions. Obviously, the safety of TMS in this setting needs to be appropriately documented first.

The combination of TMS with other neuroimaging techniques might provide another unique approach to an enhanced understanding of the mechanisms of action of TMS (Paus 1999). Ilmoniemi *et al.* (1997) showed the feasibility of studying the direct and remote effects of TMS on high-density EEG. Paus *et al.* (1997, 1998) pioneered the use of PET in the study of direct and trans-synaptic, corticocortical effects of TMS. The combination of TMS with PET of special ligands, such as dopa or GABA receptor agonists, would provide a unique opportunity of increasing our insight into the neurophysiological effects of TMS. However, it is important to realize that, in PET studies, the ligand uptake requires sometime and TMS might not be safely applicable throughout that period (Wassermann 1998). Therefore, the results of such TMS–PET combination studies might in part reflect the brain response following the stimulation rather than the effects of the stimulation itself. Recently, Bohning *et al.* (1998, 1999) succeeded in imaging the changes in brain activity on fMRI evoked by TMS. This is a technically challenging but most exciting accomplishment. Indeed, fMRI and eventually MR spectroscopy might provide information about the mechanisms of action of TMS with good temporal resolution and exquisite anatomical detail in normal humans. In addition, as MRI does not expose subjects to radioactive compounds, serial studies and within-individual comparisons will be possible. Nevertheless, the interaction of the TMS-induced magnetic field and the MRI magnetic field can cause damage to the stimulating coil posing a safety hazard and deceiving artefacts in fMRI BOLD images which might lead to false results (Chen *et al.* 1999).

Despite these problems of focality, neuroanatomical correlation and neurobiological mechanisms of action, TMS provides a unique tool for studying the causal relationships between brain activity and behaviour. TMS delivered appropriately in time and space can transiently block the function of neuronal networks, allowing for the creation of a time-dependent 'virtual lesion' in an otherwise healthy brain. Amassian *et al.* (1988, 1998) pioneered the use of this type of application of TMS in the study of the visual cortex. When applied to the occipital lobe at appropriate intensity, TMS blocks the detection of visual stimuli presented *ca.* 100 ms earlier. Day *et al.* (1989) used single-pulse TMS applied to the motor cortex during the time between the go-signal and the initiation of motor response in a reaction time paradigm to study the temporal profile of cortical activation before movement. Cohen *et al.* (1991) used a similarly designed experiment to study the timing of the contribution of the somatosensory cortex for the detection of tactile stimuli to the fingers. Similar approaches have been applied in the study of area V5 during motion perception (Beckers & Homberg 1992; Hotson *et al.* 1994) and the interaction between areas V1, V5 and V4 (Beckers & Zeki 1995; Walsh *et al.* 1998). Recently, Terao *et al.* (1998*a*) elegantly illustrated this use of TMS in revealing temporal

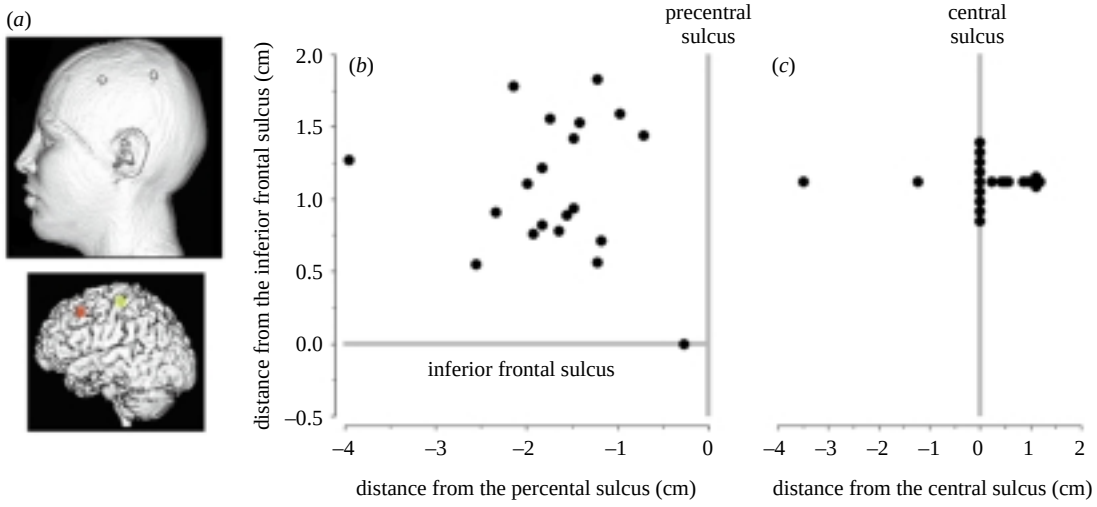

Figure 3. (*a*) Identification of the centre of the brain area directly targeted by TMS from the optimal scalp position for activation of the contralateral abductor pollicis brevis muscle (Wassermann *et al*. 1996) and from a scalp position 5 cm anterior to it and in the same parasagittal plane (Pascual-Leone *et al*. 1996*a*). The figure presents the data for 20 subjects. The position of the figure of eight coil on the scalp was marked with a vitamin A capsule and an MRI was obtained and three-dimensionally reconstructed. The location of the vitamin A capsule on the scalp was projected perpendicularly to the skull surface onto the brain surface and the point of intersection of the projection line with the brain was marked (red and yellow dots). Scattergrams display these points of intersection (brain area targeted by TMS) in relationship to the central sulcus ((*c*), 'motor cortex target') and in relationship to the pre-central and the inferior frontal sulcus ((*d*), 'prefrontal target'). Note the relatively accurate targeting of the central sulcus (primary motor area) but the large variability in the prefrontal target.

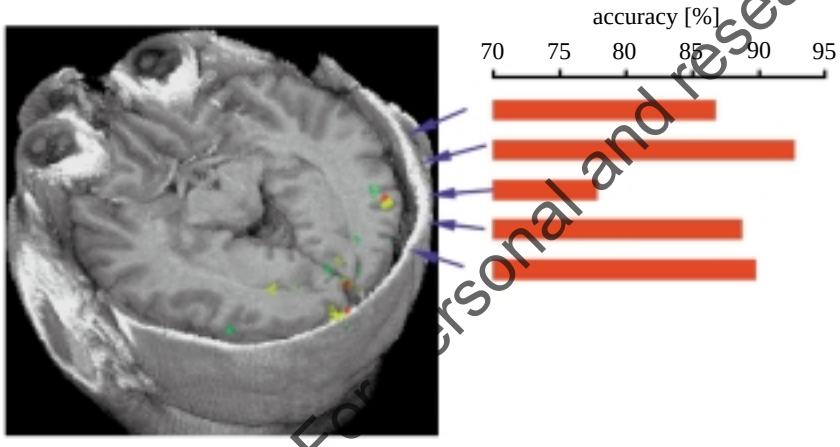

Figure 4. Results of an unpublished study by E. Kiriakoupolos, J. Barton and J. Intrilligator. A BOLD fMRI study shows the areas of activation during visual stimulation with a display of random motion (red), vection motion (green) or both (yellow). rTMS (figure-of-eight coil, 120% of motor threshold intensity, 10 Hz and maximum 2 s train) was applied to scalp positions around the area of maximal activation on the fMRI in an attempt to disrupt motion perception (Beckers & Homberg 1992; Hotson *et al*. 1994; Beckers & Zeki 1995). The bar histogram depicts the subject's mean accuracy in the detection of the direction of random motion during TMS to five different scalp positions. Note the significant decline in performance limited to the scalp position directly overlying the area of activation on the fMRI study.

correlation between activity in different cortical areas. They employed focal TMS to investigate the topography of human cortical activation during an anti-saccade task. While the subject performed the anti-saccade task, TMS was delivered to different cortical sites 80, 100 or 120 ms after target presentation. TMS to the frontal and posterior parietal regions (presumably the frontal eye fields and posterior parietal cortices, respectively) delayed the onset of the anti-saccade. Interestingly, over the parietal cortex, TMS delayed the saccade onset when it was delivered 80 ms prior to the target. However, frontal TMS delayed the anti-saccades when delivered 100 or 120 ms after target presentation. Terao *et al*. (1998*a*) concluded that, in this form of application, TMS provides a useful method of not only detecting the topography of cortical regions active during saccadic eye movement, but also of constructing a physiological map to visualize the temporal evolution of functional activities in the relevant cortical regions. Indeed, this type of application of TMS ought to be generalizable to any number of other neurocognitive processes. In this context, rTMS provides an excellent 'exploratory' tool (Pascual-Leone *et al*. 1994*b*). Single-pulse TMS studies require both temporal and spatial knowledge: where to stimulate and when. In contrast, rTMS can be safely applied over a fairly large time-window thereby providing an opportunity of testing the contribution of a cortical area to a given task without stringent temporal constraints. This type of application can be used to study hemispheric dominance for language (Pascual-Leone *et al*. 1991; Epstein 1998) or memory (Grafman *et al*. 1994), frontal contributions to working memory or procedural learning (Pascual-Leone *et al*.

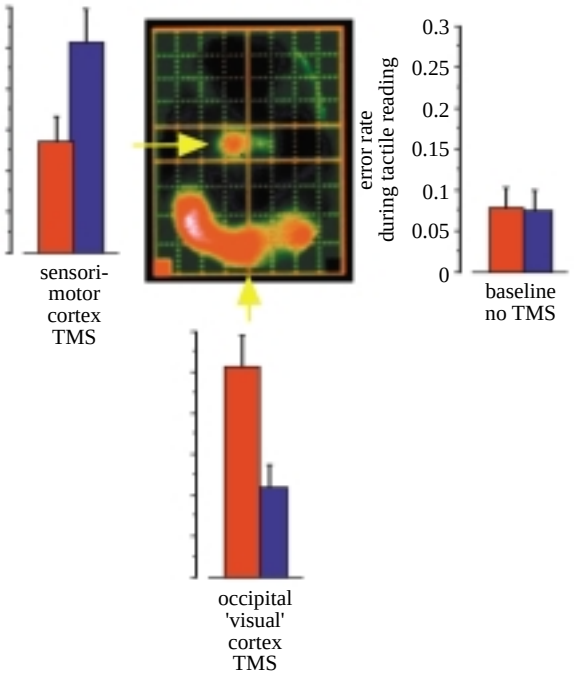

Figure 5. Activation on PET of the contralateral sensorimotor cortex and the occipital cortex in an early blind subject during Braille reading (Sadato *et al*. 1996). TMS was then applied to a series of scalp positions in order to test the causal relation between activation on PET and tactile Braille reading systematically (Cohen *et al*. 1997). Note the significant increase in errors during tactile discrimination of embossed Roman letters induced by TMS to the sensorimotor cortex in sighted controls (blue columns). In contrast, note the relatively minimal effects of sensorimotor TMS but the large effect of occipitopolar TMS on tactile reading ability in early and congenitally blind subjects (red). Error bars represent the standard error of the mean. A large number of other, control scalp positions were targeted by TMS and shown not to influence tactile reading ability in either group of subjects. Modified from Sadato *et al*. (1996) and Cohen *et al*. (1997).

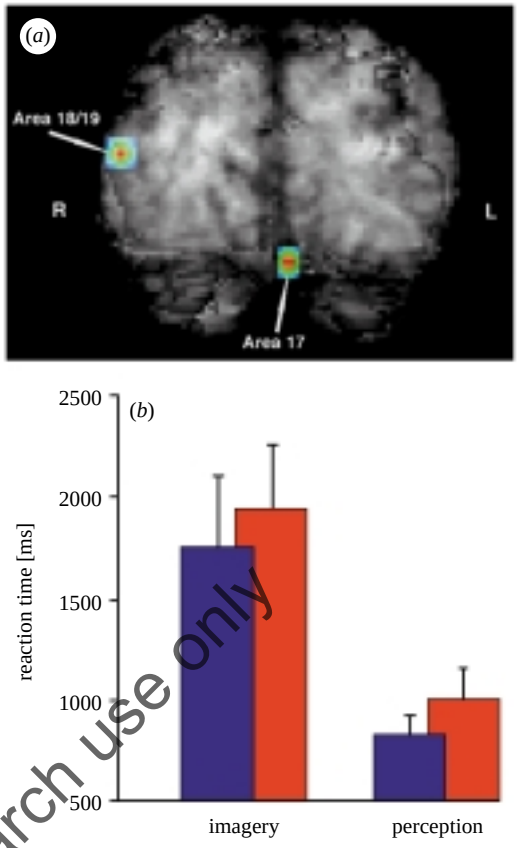

Figure 6. Study of the role of the primary visual cortex during depictive visual imagery combining PET and TMS. Modified from Kosslyn *et al*. (1999). (*a*) The results of PET scanning illustrate the activation in area 17 during imagery compared to baseline. Activation in areas 18/19 on the right can also be seen in this slice plane. The strength of the Z-scores is illustrated according to colour, with blue, green, yellow and red representing increasingly high Z-scores; in this slice plane, the highest Z-score, located within area 17, is 3.31. (*b*) The column histograms display the reaction time results when low-frequency rTMS was delivered prior to the imagery and perception conditions. The effects of real rTMS (red) were compared with those of sham rTMS (blue). A two-way repeated ANOVA on the response times revealed a main effect of stimulation (real versus sham rTMS) and modality (imagery versus perception). Contrasts revealed that the response times during real rTMS were significantly greater than those during sham rTMS in both imagery and perception. This response time increase was observed in all five subjects in both conditions.

1996*b*), or the role of parietal structures in hemi-inattention (Pascual-Leone *et al*. 1994*a*). Cohen *et al*. (1997) elegantly demonstrated the use of this form of application of rTMS in a study of the functional significance of striate cortex activation during tactile Braille reading in early and congenitally Braille subjects. Using PET, Sadato *et al*. (1996) described activation of the primary 'visual' cortex in early blind readers when performing tactile spatial discrimination tasks and reading Braille. Subsequently, Cohen *et al*. (1997) demonstrated that rTMS to V1 greatly impaired blind subjects' Braille reading ability while it did not affect the ability of sighted controls to identify embossed Roman letters haptically (figure 5). Indeed, in the blind subjects rTMS to the occipital cortex resulted in a greater disruption of tactile Braille reading than rTMS to the somatosensory cortex contralateral to the reading hand (figure 5).

rTMS appears to be able to modulate the level of excitability of a given cortical area beyond the duration of the rTMS train itself (Chen *et al*. 1997; Berardelli *et al*. 1998; Pascual-Leone *et al*. 1998). Remarkably, depending on the stimulation frequency and intensity, it seems possible to potentiate or depress cortical excitability (Pascual-Leone *et al*. 1998). This lasting effect of TMS allows the study of the causal link between focal brain activity and behaviour without the potential disruption of ongoing TMS during the task. In this design, behaviour is evaluated before and following rTMS (rather than during rTMS). Such a design has the advantage of avoiding a non-specific disruption of performance due to discomfort, noise, and muscle twitches associated with TMS during the task. Kosslyn *et al*. (1999) used this lasting effect of rTMS on cortical excitability to demonstrate that depictive visual imagery requires normal function of area 17 (figure 6). Subjects memorized a display that contained four quadrants, each with a set of stripes. These sets of stripes differed in a variety of dimensions (for example, stripe thickness or length). In a first experiment, the subjects underwent a PET scan as they closed their eyes and visualized the display. They then heard two numbers,

which they had previously learned were labels for specific quadrants, followed by the name of a dimension (such as 'length'). They were to decide whether the set of stripes in the first-named quadrant was greater along that dimension than the set of stripes in the second-named quadrant. The resulting brain activation was compared to a control condition in which the same type of auditory stimuli were delivered but no imagery was used. This PET study revealed that area 17 was activated during the visual imagery task (other areas were also activated but they are not relevant for the present issue). In a second experiment, subjects were tested on the imagery and on the perceptual version of the same task before and following modulation of the activity in area 17 using 1 Hz rTMS. After presumed suppression of cortical excitability in area 17 by 1 Hz rTMS, subjects showed a significantly worsened performance both in the perceptual and in the imagery versions of the task. Therefore, the PET results showed that when patterns of stripes are visualized, area 17 is activated, and the rTMS results showed that such activation is used in information processing.

The possibility of enhancing behaviour by applying rTMS at parameters that may potentiate cortical excitability is intriguing and could have a profound impact on neurorehabilitation and skill acquisition (Pascual-Leone *et al*. 1999). However, pertinent data in this regard are still few and largely preliminary.

This modulation of cortical excitability beyond the duration of the rTMS train itself raises the possibility of exploring the potential therapeutic uses of rTMS (George *et al*. 1999). A variety of neuropsychiatric conditions are associated with disturbed cortical activity as documented by neuroimaging and neurophysiological studies. 'Forced normalization' of such disturbed cortical excitability might lead to a symptomatic improvement. Remarkably, in the case of major depression, several studies have shown such a beneficial effect of TMS which seems to last for days, weeks and possibly even months (Pascual-Leone *et al*. 1998; George *et al*. 1999). This long duration of effects raises a number of new questions regarding the mechanisms of action of TMS. If indeed TMS is shown to have therapeutic effects in neuropsychiatry the potential benefit for patients will probably be sizeable given the very mild side-effect profile. On the other hand, the careful study of such effects promises, regardless of the final outcome, to enhance our knowledge of the pathophysiology of a variety of neuropsychiatric illnesses.

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