# Transcranial magnetic stimulation in cognitive neuroscience – virtual lesion, chronometry, and functional connectivity

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Fifteen years after its introduction by Anthony Barker, transcranial magnetic stimulation (TMS) appears to be 'coming of age' in cognitive neuroscience and promises to reshape the way we investigate brain–behavior relations. Among the many methods now available for imaging the activity of the human brain, magnetic stimulation is the only technique that allows us to interfere actively with brain function. As illustrated by several experiments over the past couple of years, this property of TMS allows us to investigate the relationship between focal cortical activity and behavior, to trace the timing at which activity in a particular cortical region contributes to a given task, and to map the functional connectivity between brain regions.

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**Abbreviations**

| | |
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| **CBF** | cerebral blood flow |
| **EEG** | electro-encephalography |
| **GABA** | γ-aminobutyric acid |
| **PET** | positron emission tomography |
| **rTMS** | repetitive TMS |
| **TMS** | transcranial magnetic stimulation |

## Introduction

The investigative tools used in science determine the kinds of empirical observations that can be made. Very often, the results produced by new tools in the neurosciences force us to re-evaluate models of brain–behavior relationships and even affect the kinds of questions that are asked. For example, over the past decade, the neuroimaging techniques of computerized tomography, magnetic resonance imaging, positron emission tomography (PET), magneto-encephalography and electro-encephalography (EEG) have shaped the way in which we model behavior. Anatomical neuroimaging techniques have produced ever more detailed descriptions of the extent of lesions produced by brain injury. Combining this knowledge with clinical examination of the affected patients should provide insights into the original function of the damaged brain areas. However such a 'lesion study approach' is hampered by the issue of compensatory plasticity, and by the possibility that the disturbance to function may be more, or less, widespread than the anatomical lesion [1]. Functional neuroimaging methods have overcome some of these problems and can demonstrate an association between behavior and patterns of activity in cortical and subcortical structures. Although careful design of experiments may allow us to conclude with reasonable certainty that the correlation of brain activity with behavior is attributable to a causal connection (i.e. that the brain activity causes the behavior), imaging alone will never be able to provide proof of that assertion.

Transcranial magnetic stimulation (TMS) is based on Faraday's principles of electromagnetic induction. A pulse of current flowing through a coil of wire generates a magnetic field. If the magnitude of this magnetic field changes in time, then it will induce a secondary current in any nearby conductor. The rate of change of the field determines the size of the current induced. In TMS studies, 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 with negligible attenuation (only decaying by the square of the distance). This time-varying magnetic field induces a current in the subject's brain, and this stimulates the neural tissue. In many experiments, single pulses of stimulation are applied. Each of these lasts about 100 μs, so that the effect is similar to stimulating a peripheral nerve with a conventional electric stimulator. To date, the single-pulse technique appears to be completely safe when applied to healthy individuals. It is also possible to apply a series of pulses at rates of up to 50 Hz (this is known as repetitive TMS, or rTMS). This procedure is more dangerous and can cause seizures even in healthy subjects; because of this risk, safety and ethical guidelines must be followed [2••].

Although studies in animal models and, particularly, in neurosurgical patients have provided considerable insight into the mechanisms of action of TMS [3,4,5•,6•,7,8•], our knowledge is still limited [1,9,10]: we are not yet able to ascertain precisely the depth of stimulation in the brain, nor its spatial resolution; we are not able to determine which neural elements are the most sensitive to stimulation in a particular area of brain; and we are not certain whether all the effects of stimulation are attributable to activity at the site of the stimulus or whether activity spreads through neural pathways to other more distant sites.

One might therefore be tempted to wait for greater insights into the neuronal effects of TMS before applying it widely to studies in cognitive science. We would argue that waiting may be desirable, but is not necessary. As we

shall see below, the majority of TMS experiments in cognitive science rely on the fact that magnetic stimulation of an area of the brain disrupts any processing that is going on at the time. If that processing is contributing to behavior, then we would expect to observe deterioration in the performance of that behavior. From such an observation, we can conclude that there is a functional connection between the activity and the behavior. In this scenario, we need not know precisely which elements in the brain were activated by the stimulus. Any artificially induced synchronized activity in a population of neurones will interfere with their function — at this fundamental level, we can probably trust the technique. In fact, by analogy with the synchronised spike-wave discharges of an epileptic focus, it seems probable that a large magnetic stimulus will synchronously excite a population of neurones. These will fire a rapid series of impulses for a few milliseconds, and then the whole activity will be suppressed by a long-lasting period of (GABAergic) inhibition. The whole process may last between 20 and 200 ms, depending on the intensity of the stimulus.

In this review, we shall highlight two of the major potential contributions of TMS studies to our understanding of cognitive neuroscience: the transient disruption of focal cortical activity to establish the causal role and the timing of the contribution of a given cortical region in a behavior, and the application of TMS to the study of functional brain connectivity. What is critical and common to both of these contributions is that they allow us to further our knowledge beyond that which the study of patients can teach us — they allow us to empirically test specific neuropsychologic models and constructs.

## What does it do and when does it do it? A causal chronometry of brain function

Applied as single pulses appropriately delivered in time and space, or applied in trains of repetitive stimuli at an appropriate frequency and intensity, TMS can be used to transiently disrupt the function of a given cortical target, thus creating a temporary 'virtual brain lesion' [1,11]. This makes it possible to study two aspects of the contribution of a given cortical region to a specific behavior: 'what does it do?' and 'when does it do it?'.

An early example of the use of TMS to assess the causal significance between focal brain activity and behavior was the study by Cohen *et al.* [12] of the role of the visual cortex during tactile Braille reading in early blind subjects. Functional imaging studies of early or congenitally blind subjects reveal that their primary visual cortex can be activated by Braille reading and other tactile discrimination tasks [13]. This activation could be either an epiphenomenon of tactile information processing in blind people (regardless of whether related to compensatory mechanisms or not), or causally related to the tactile spatial discrimination ability of the subjects. Cohen *et al.* [12,14•] used TMS to disrupt the function of different cortical areas in blind subjects and sighted volunteers while they used their index finger to read Braille or embossed Roman letters. TMS of the occipital visual cortex (centred over the striate cortex, area V1) induced reading errors and distorted the tactile perceptions of congenitally or early blind subjects, but did not affect performance in the sighted controls or in those subjects who became blind after age 14 (if the blindness was slowly progressive in onset or if its extent was partial) [14•]. Hamilton *et al.* [15] have reported the notable case of an early blind woman who suffered bilateral occipital damage following an ischemic stroke. She became unable to read Braille despite her somatosensory perception being otherwise unchanged. This experiment of nature parallels the effects of TMS and, again, demonstrates that the visual cortex is required for tactile spatial processing by early blind subjects.

Other recent examples of studies using 'virtual lesions' to establish the causal role of a cortical region for a given behavior are the studies of Kosslyn *et al.* [16••] on primary visual cortex in visual imagery, Ganis *et al.* [17] on motor cortex in mental rotation, Zangaladze *et al.* [18••] on peristriate visual cortex in tactile discrimination of orientation, and Jahanshahi *et al.* [19,20] on frontal cortex in random number generation.

In the majority of these experiments, a series of stimuli was applied at a frequency of 20 Hz over a period of 2 s, with the result that the data could yield information only on the parts of the brain that are important for performing a particular task. However, if single stimuli are applied — which disrupt activity for only a short time — it is possible to obtain information on precisely when activity contributes to task performance (i.e. the 'chronometry' of cognition). For example, in a variation on the Braille reading studies [21], real or non-sensical Braille stimuli were presented to the pads of the reading (index) fingers of early blind subjects with a specially designed Braille stimulator. Single-pulse TMS to the contralateral somatosensory cortex disrupted detection of Braille stimuli when it was applied at interstimulus intervals of 20 to 40 ms; the subjects did not realize that a peripheral stimulus had been presented. In contrast, TMS to the striate cortex disrupted the processing of the Braille stimuli when it was presented at interstimulus intervals of 50 to 80 ms: the subjects typically were aware that a peripheral stimulus had been presented, but were unable to discriminate what particular Braille symbol it was. This suggests that the TMS caused interference with their perception of the Braille symbols (i.e. subjects knew that they had been presented with a Braille symbol, but could not tell which one it was).

Several other recent studies using TMS have provided information about which cortical area contributes to performance in a specific task, and at what precise moment the contribution is critical. Zangaladze *et al.* [18••] investigated both the involvement of peristriate visual cortex activity during discrimination of the orientation of tactile

gratings in normal subjects, and the timing of this involvement. It was found that the contribution of the peristriate visual cortex to performance on the task could be abolished by TMS stimulation presented 180 ms after presentation of the tactile stimulus — thereby suggesting that the timing of tactile input to the peristriate visual area occurs 180 ms after stimulus presentation. Terao *et al.* [22] investigated the contributions of the frontal and parietal cortex to an antisaccade task. They delivered focal TMS at various time intervals (80, 100, and 120 ms) after target presentation over various sites on the scalp while the subjects performed an antisaccade task. Saccade onset was significantly delayed by TMS to frontal and posterior parietal regions of either hemisphere. The frontal region corresponded to the frontal eye field, whereas the parietal region included the posterior parietal cortex. The timing of the TMS effect was earlier (80 ms) for the posterior parietal region and later for the frontal region (100 ms). This suggests an information flow from posterior to anterior cortical regions during the presaccadic period. Schulter *et al.* [23,24••] studied the timing of the involvement of the premotor and the primary motor cortex in a choice reaction time task. Subjects performed a cued movement task while receiving single-pulse TMS to three possible sites: sensorimotor cortex, posterior premotor cortex or anterior premotor cortex. TMS slowed movements when applied at 140 ms after the visual cue over the anterior premotor site, at 180 ms after the visual cue over the posterior premotor site, and at 220 ms and later after the visual cue over the sensorimotor cortex. These results are consistent with a change from signal- to movement-related processing when moving from premotor to motor cortex. In a second experiment the authors introduced a preparatory set period between an instruction signal, which informed subjects which movement to make, and a 'Go' signal, which informed them when to make the movement. In this case, TMS slowed movements equally regardless of whether the anterior premotor or the sensorimotor cortex was targeted. Therefore, the findings suggest that set activity is processed by both premotor and motor cortices.

## Taking TMS to the patients

### Therapy

It is possible that TMS may be used to treat neuropsychological patients. We shall not address this topic directly, however, as most of the relevant work involves neuropsychiatric disorders and is still preliminary [25–27]. Interestingly, TMS not only can disrupt, but also can functionally enhance activity in a targeted cortical region [28]. Topper *et al.* [29] found that the application of a single pulse of TMS to Wernicke's area speeded reaction times for picture naming, suggesting that this behavioral gain resulted from enhanced excitability in Wernicke's area as a result of TMS. However, at the present time it is difficult to understand why the effect was maximal when stimuli were applied 500 ms or 1 s prior to presentation of the picture. Such a long-lasting effect of a single magnetic stimulus of cortical circuitry has never been observed before. One possible mechanism to account for such long delays might be that the effects of TMS are not caused by the stimulation of the directly targeted Wernicke's cortex, but rather are attributable to effects on more distant cortical regions reached by transsynaptic cortico-cortical effects.

### Study

TMS can also be used to explore the compensatory cortical plasticity that occurs in response to a lesion. Particularly elegant examples of such work are the studies of Olivieri *et al.* [30,31••] on neglect. In an initial study [30], they asked normal control subjects to report detection of very weak electrical stimuli applied to the first, third and fifth digits of either hand or both hands. Single-pulse TMS over the right parietal cortex 20 or 40 ms after digit stimulation reduced the subjects' ability to detect input from either hand, particularly if both hands were stimulated at the same time. Applying TMS to only the left parietal cortex had a similar but smaller effect, whereas stimulation of frontal cortex had no effect. Olivieri *et al.* concluded that normal controls have a right hemisphere dominance for stimulus perception, and that parietal regions are active in this process 20 to 40 ms after stimulus presentation.

Olivieri *et al.* [31••] then applied TMS to patients with right-hemispheric lesions. When stimuli were applied simultaneously to both hands, the patients often failed to detect the stimulus on the left side. Stimulation (at intensities 10% higher than those used in normal subjects) of left frontal, but not of parietal cortex, significantly reduced the rate of extinction (i.e the lack of detection of the stimulus). Therefore, as in animal models of neglect [32], transient disruption of the healthy hemisphere restores spatial attention to the contralesional side, thereby improving neglect. These results support the notion that spatial attention may be explained in terms of interhemispheric competition between subcortical and cortical structures; this competition may be asymmetrical [33]. Furthermore, it may be possible to use TMS — or perhaps rTMS — to induce long-lasting changes in cortical excitability for the rehabilitation of neglect patients.

## Going beyond the patients

TMS can also provide insight into brain function beyond that which can be obtained from lesion studies in patients. A good example of TMS being used in this way are the recent experiments by Walsh *et al.* [34,35••] on parietal cortex function and conjunction search tasks. Consistent with findings in patients with right parietal lesions, they [34] found that TMS applied to the right parietal cortex disrupts performance of controls on a color and form conjunction search task. Interestingly, however, they also noted a persistent — though later — engagement of the parietal cortex when no target was given during a trial and the subject decided to terminate the search rather than guess the answer.

This study demonstrates the usefulness of TMS because the specificity of the contribution of parietal cortex to perceptual learning during conjunction tasks is normally difficult to test in patients, given that lesions cannot be reversed (see [34]). Using TMS, however, it is possible to disrupt performance of a novel task while demonstrating the lack of impairment in another, overlearned conjunction task (i.e. a conjunction task in which performance has become partially automatized as a result of extensive practice). Hence, the parietal lobe contribution is specific for performance when a task is novel — or at least not practiced so extensively that it might have become automatized.

A final example of how TMS studies can take us 'beyond patients' is provided by the effects of transient parietal (visual motion area V5) disruption during color and motion conjunction search tasks [35••]. The disruption to neural activity caused by TMS is both transient and acute, hence not allowing plastic reorganization of the brain. Walsh *et al.* [35••] found that patient LM, who has bilateral V5 lesions, is able to perform form and color conjunction tasks. It is not clear, however, what are the effects of the lesions to V5 with respect to LM's relatively preserved abilities. When TMS is used to transiently disrupt V5 in normal controls, performance on form and motion conjunction tasks deteriorates, but subjects show improved performance on color and form conjunction tasks. Therefore, TMS is providing insights into the interplay between functionally connected areas by unmasking such paradoxical performance improvements.

## How is it all connected? Brain–behavior relations as a mobile sculpture

Paus *et al.* [36,37,38••] were the first to introduce the combined techniques of TMS and functional neuroimaging as a means of mapping neural connections in the live human brain. They used TMS to stimulate directly a selected cortical area; simultaneously, they measured changes in brain activity, indexed by cerebral blood flow (CBF), using PET. Ilmoniemi *et al.* [39] used a similar approach for studying cerebral connectivity using a combination of TMS and quantitative EEG.

In their first study, Paus *et al.* [36] applied TMS to the left frontal eye fields and found a significant positive correlation between the number of TMS pulses and CBF at the stimulation site and, most importantly, in the superior parietal and medial parieto-occipital regions. The pattern of these distal effects was consistent with the known anatomical connectivity of monkey frontal eye fields. The authors conclude that the combination of TMS with functional neuroimaging "offers an objective tool for assessing the state of functional connectivity without requiring the subject to engage in any specific behavior" [36]. Curiously, the frontal eye fields are also richly connected to area 46 in the prefrontal cortex and to motor cortical areas, but these were not activated. We wonder whether covert, implicit behavior, such as concentrating on inhibiting eye movements, might prime certain connections and hence influence the effects of TMS.

In a second study, Paus *et al.* [37] again used a combination of TMS and PET, but on the primary motor cortex and using differing numbers of stimuli that were below the motor threshold. In this case, activations were observed at a distance — in the supplementary motor area, the parietal cortex and the contralateral motor and premotor areas. However, unlike the frontal eye fields data, these results showed negative correlations between blood flow and the number of TMS pulses. This was interpreted as indicating that the low-intensity stimuli that were applied to the motor cortex had an inhibititory effect in this area. Whatever the explanation, it is a warning that stimulation may have subtly different effects on different regions of the brain.

As Lomber [32] has argued in his discussion of experiments using cooling probes, it is important to realize that transient disruption of a given cortical region tells us mostly about the capacity of the rest of the brain to adjust (i.e. react or adapt) to it. Hence, 'functional connectivity experiments' combining TMS with functional imaging might in fact reveal the capacity of the brain to rapidly adjust to the disruption of a given area in an attempt to maintain function. Mottaghy *et al.* [40] have recently illustrated this point in a study in which TMS and PET were combined in order to investigate the role of prefrontal cortex in working memory. Performance in the task is equally disrupted by TMS to the left or to the right dorsolateral prefrontal cortex. However, PET reveals significant differences in the brain activity associated with task performance between TMS applied to the left and to the right side of the brain.

These results demonstrate for the first time the ability of TMS to produce temporary functional lesions in different elements of a neuronal network, and to demonstrate how such effects are associated with differential behavioral consequences that can be explained on the basis of the pattern of brain activity in the elements of the network that are not directly targeted by TMS. So, for example, both left and right prefrontal TMS affect performance in the working memory task. However, performance is more impaired, both in severity and duration, following right-sided TMS. The PET study of the task performance during TMS reveals that TMS to the left dorsolateral prefrontal cortex only causes significant reductions in cortical activity in the directly targeted prefrontal region. However, TMS to the right prefrontal cortex significantly reduces activity in the right prefrontal region, the right fronto-temporal pole, and bilateral parietal regions. These kinds of experiments combining TMS, behavioral measures, and functional brain imaging, allow us to model behavior by tracking the coordinated changes of activity over a widely distributed network, and to use TMS to transiently modulate elements of the network to evaluate the dependent changes throughout. It is as though we might be lightly tapping elements of a mobile sculpture in order to capture its aesthetic value in the induced swings and sways.

## Conclusions

Our knowledge about the mechanisms of action of TMS is still limited. Nevertheless, its limitations aside, TMS provides us with a unique opportunity to study brain–behavior relations. TMS can create virtual lesions, thereby allowing us to obtain information about the timing of the contribution of a given cortical region to a specific behavior ('causal chronometry'). Furthermore, combined with functional neuroimaging, TMS can be used to study functional connectivity and, in particular, to study the distributed effects of TMS on the neural networks involved in a given behavior. TMS is a timely addition to the armamentarium of cognitive neuroscience tools and may change the way we approach problems of linking brain activity with behavior.

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