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TIMELINE

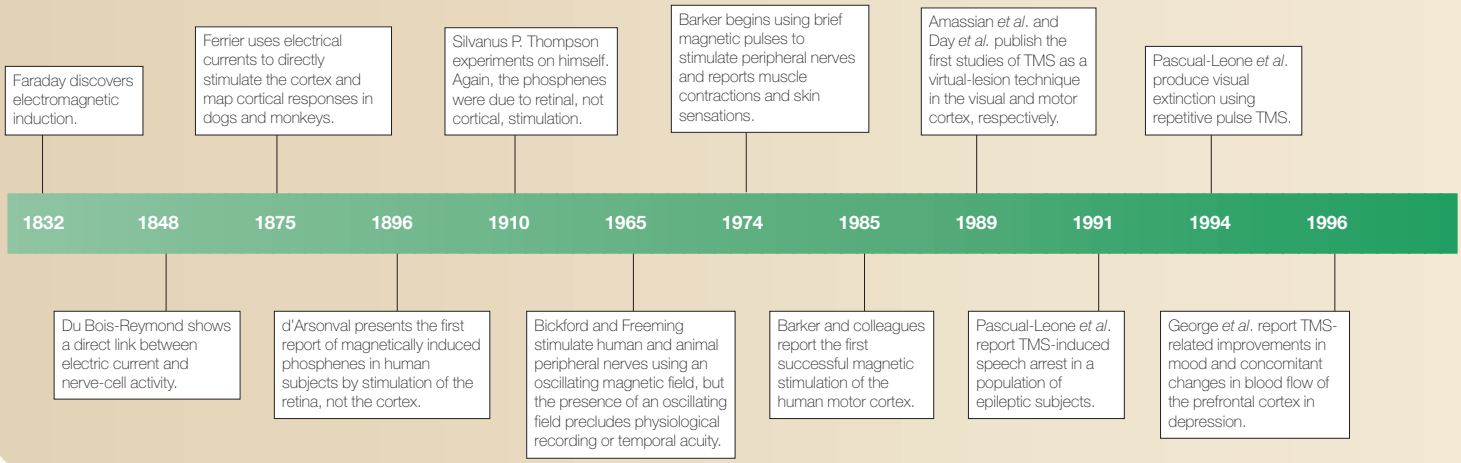
Transcranial magnetic stimulation and cognitive neuroscience

Vincent Walsh and Alan Cowey

Transcranial magnetic stimulation has been used to investigate almost all areas of cognitive neuroscience. This article discusses the most important (and least understood) considerations regarding the use of transcranial magnetic stimulation for cognitive neuroscience and outlines advances in the use of this technique for the replication and extension of findings from neuropsychology. We also take a more speculative look forward to the emerging development of strategies for combining transcranial magnetic stimulation with other brain imaging technologies and methods in the cognitive neurosciences.

Transcranial magnetic stimulation (TMS) is now an established investigative tool in the cognitive neurosciences[1–5], and several groups have begun to exploit its potential in the study of perception[6–16], attention[16,17], learning[18,19], plasticity[20–24], language[25–27] and awareness[28,29]. It is also finding applications in the study and treatment of movement disorders[30–32], epilepsy[33,34], depression[35–38], anxiety disorders[39–41], stuttering[42,43] and schizophrenia[44–47] (TIMELINE). Despite the breadth and depth of the published research, the considerations behind the use of TMS and its value in addressing neuropsychological questions remain poorly understood. In this article we confront some of the most common confusions about TMS and show how it can be used to complement and extend existing techniques. The use of TMS in clinical neurophysiological studies is highly advanced and has been reviewed elsewhere[48]. Likewise, parameters for the safe use of TMS have been established and have been documented extensively in other sources that are required reading for those contemplating the use of TMS[49–51]. Our aim is not to provide a technical introduction (which can be found in REFS 52–54). Here we focus on the role of TMS in the cognitive neurosciences and propose a conceptual framework for the future application of TMS to this area (FIG. 1).

Timeline | **TMS in cognitive neuroscience**



TMS and the brain

TMS operates on Faraday's principle of electromagnetic induction. Faraday showed that an electrical current passed through one coil could induce a current in a nearby coil. The current in the first coil produces a magnetic field that in turn causes current to flow in the second coil. In TMS that second coil is replaced by brain tissue and the induced electric field elicits neuronal activity (FIG. 2). The key features of the technique are that the TMS machine delivers a large current in a short period of time — the current in the TMS coil then produces a magnetic field which, if changing rapidly enough, will induce an electric field sufficient to stimulate neurons[52–54] or change the resting membrane potentials in the underlying cortex. In short, TMS can be used to induce a transient interruption of normal brain activity in a relatively restricted area of the brain.

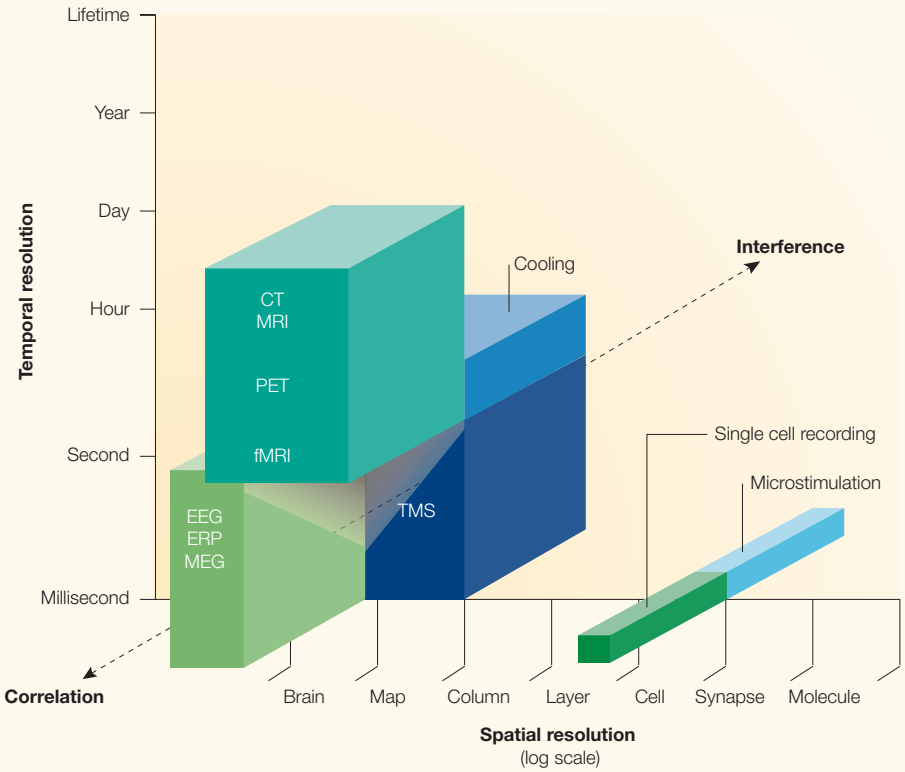
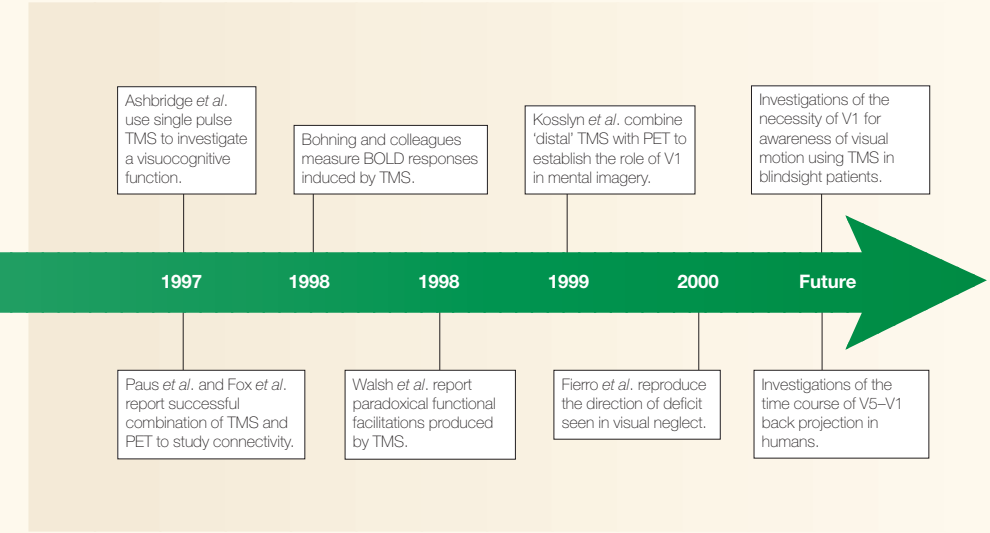


Figure 1 | **Defining the problem space of TMS.** The place of TMS in neuropsychological studies is best thought of as the 'problem space' it occupies. This figure shows the spatial and temporal resolution of TMS compared with other techniques. However, it is not just the spatial and temporal selectivity that make TMS a useful experimental approach; it is the ability of TMS, like cooling and microstimulation, to transiently interfere with brain functions. In contrast, existing neuroimaging techniques provide correlative data. Clearly, when one selects a technique, one is also making a selection about the kind of question one can ask. CT, computerized tomography; EEG, electroencephalography; ERP, event-related potential; MEG, magnetoencephalography; fMRI, functional magnetic resonance imaging; PET, positron emission tomography.

The mechanism of interference. Perhaps the most common source of confusion over TMS is exactly how it interferes with cortical information processing to induce such a temporary lesion. As far as neuropsychological studies are concerned, the effect of TMS can be thought of as inducing 'noise' into neural processes. If a group of neurons are involved in a given task (for example, identifying a shape or matching a picture to a word), introducing a TMS pulse is highly unlikely to selectively stimulate the same coordinated pattern of neural activity as performance of that task. Rather, TMS induces activity that is random with respect to the goal-state of the area stimulated. In other words, TMS induces disorder rather than order into the information processing system, thereby disrupting task performance. This 'neural noise' concept underpins what has become known as the 'virtual patient' approach[1–4]. By careful application, TMS can be used to transiently recreate the deficits seen in some neuropsychological patients, or can be used to create deficits that are rarely, if ever, obtained in neurological patients.

Spatial resolution. Another important source of confusion is the spatial resolution of TMS. The magnetic field produced by TMS is not spatially focal (in theory it is of infinite extent, like the earth's gravitational field). However, the distribution of the induced electric field can and has been modelled[55–57], and progress has been made in relating the induced currents to specific sites of activation with a



resolution of a few millimetres. Indeed, there are now both indirect and direct demonstrations of the considerable specificity that can be achieved by this technique. Consider the indirect case first. The spatial and functional localization of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are achieved, in part, by comparing the effects on blood flow of different task conditions. The final spatial locations of, for example, 'the motion area'[58], or an area important for memory processes[59] or processing words[60], are then inferred from the differences between the activations produced by task conditions that vary only in the process under consideration. Similar inferences can be applied to TMS. Here, however, the number of sites that can be compared is more restricted. This limitation provides a conceptual constraint on the application of TMS because a hypothesis is required for every comparison. The subtraction approach follows the logic of lesion analysis in humans and non-human primates, and that of functional neuroimaging.

In most studies of cognitive function the TMS coil will be a figure-of-eight shape, which induces a maximum electrical field that peaks under the intersection of the two windings[61–63]. The efficacy of the TMS pulse depends, in part, on the orientation of the underlying cell bodies and fibres with respect to the flow of the induced current. So, to increase confidence in the localization of effective stimulation, one can compare the behavioural effect of stimulation at several stimulation sites as described above, and determine the localization of the behaviour in question by subtractive inference (FIG. 3).

Alternatively, one can use a task control. Using task controls is of particular interest in cognitive studies as it may be sufficient to show that two processes are functionally dissociated in space or time. Anatomy and function can, however, be combined in TMS studies and some recent advances in combining TMS with neuroimaging testify to its functional precision. The first combined studies of TMS and PET[64,65] showed that TMS induced neuronal activity under the site of stimulation, but that in addition, it also had effects at anatomically connected sites distant from the coil (much as a stimulus in an imaging experiment will activate many regions of the brain). Such studies may therefore have a future use in determining the functional connectivity of the human brain[64]. More recent work has shown that the effects of TMS at the primary site correspond impressively with the activation produced by self-induced behaviour. For example, Seibner *et al.*[66] applied 2 Hz repetitive pulse TMS (rTMS) over the left sensorimotor cortex of subjects at 140% of the motor threshold. They also asked subjects to imitate the arm movement caused by the rTMS and compared changes in regional cerebral blood flow in the two conditions. Both voluntary and TMS-induced movement increased blood flow in the motor cortex contralateral to the arm movement, but voluntary movement also elicited greater activity in the supplementary motor area (FIG. 4). But both conditions excited the same connected cortical areas. George and colleagues[67–69] have also shown the similarity of brain activations caused by voluntary and TMS-induced movements. So it is clear that TMS could be used to examine changes in connectivity as a function of learning in cases where the areas activated by action and TMS are in correspondence.

There are, however, several constraints that should guide the design of TMS experiments. One important constraint on TMS is that the effects of stimulation are limited to superficial cortical regions and cannot be used to investigate functions of medial cortex or subcortical structures. One should also be aware that stimulating deeper cortical structures (for example, in the sulci) may also stimulate overlying cortex. A potential solution to this problem is to stimulate areas that are accessible in non-human primates but not in human subjects. However, this nascent branch of TMS research has other problems to overcome, such as the more rapid heating of the smaller coils used for work in smaller primates.

Temporal resolution. In cognitive neuroscience the chronometrics of information processing are central to many theories and experiments[70–74]. For cognitive studies then, an understanding of the temporal resolution of TMS is at least as important as an account of its spatial selectivity. When a TMS pulse is delivered over an area of cortex, the effect is to simultaneously activate many neurons. At the point of maximal activation, the stimulated area will have its lowest signal-to-noise ratio with respect to the task it is trying to perform. However, as neurons recover, the signal will increase, and whether or not TMS continues to have an effect will depend on the level of signal required for the task. Note that the interaction between the TMS signal and the contribution of an area to a task makes it highly unlikely that the time at which TMS has its maximal effect will correspond with the peak times reported in event-related potential (ERP) or subtractive or magnetoencephalographic (MEG) experiments (FIG. 5). An effectively disruptive pulse will interfere with processes that contribute to the build up of the ERP/MEG signal, so if the signal represents a neural event that is essential to the task, the time of TMS interference will typically precede ERP peaks and is more likely to coincide with single unit data[23]. In other words, where an ERP result reports a peak at, say 300 ms, this may reflect the contribution of more than one neural event with a group maximum at 300 ms. When TMS is applied over the areas that contribute to this signal, it may disrupt processing of the individual components that may be maximal before, at, or after the reported peak at 300 ms.

Neuropsychology and TMS

Studies of neuropsychological patients have provided some of the most important revelations of brain–behaviour relationships in the past century. They have made important contributions to the backbone of our understanding of the temporal lobe memory systems[75], the visuospatial functions of the parietal lobes[76], the different roles of the two cerebral hemispheres[77], the role of occipital lobes in

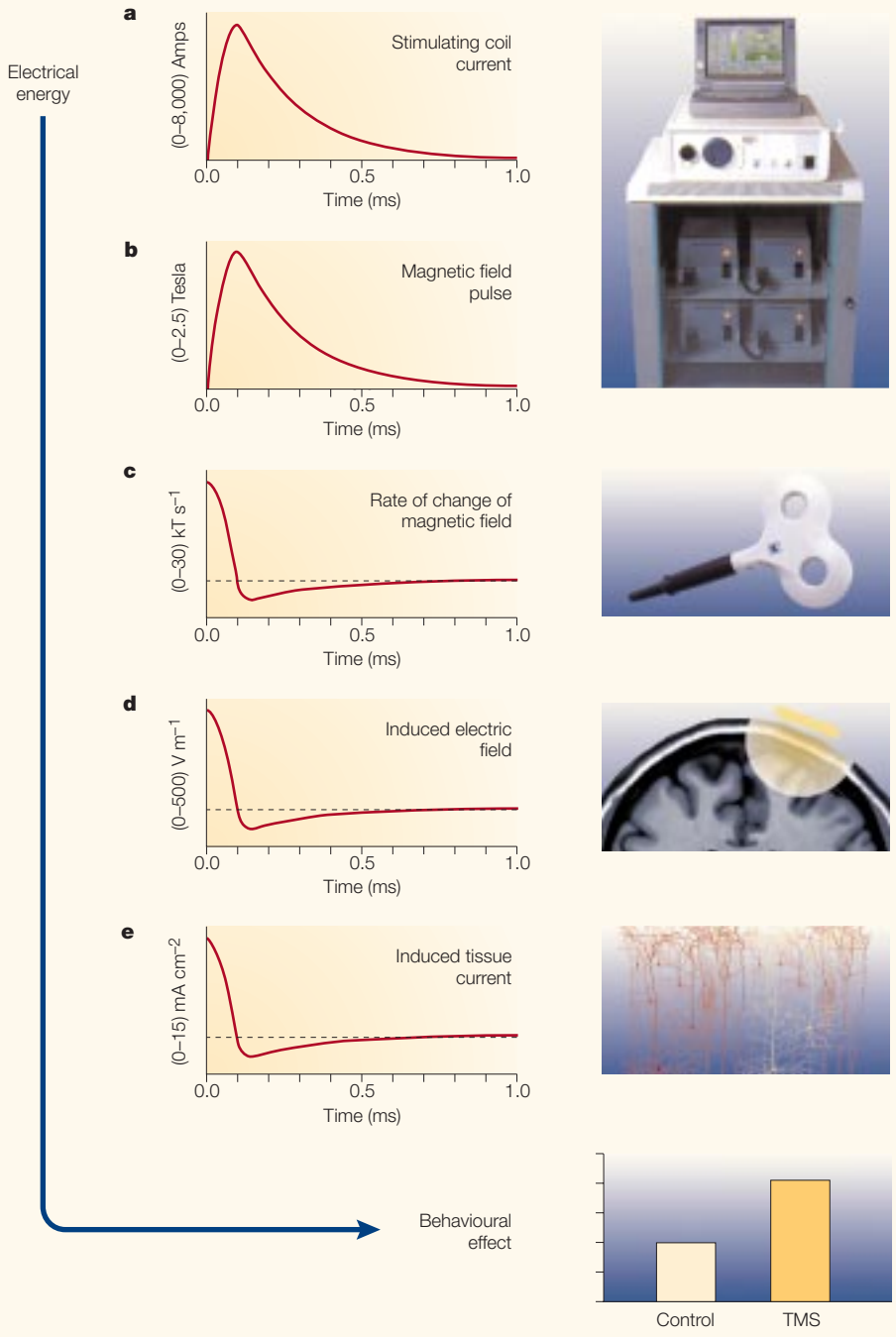


Figure 2 | **TMS and the brain.** An electrical current of up to 8 kA is generated by a capacitor (**a**) and discharged into a circular, or figure-of-eight shaped, coil which in turn produces a magnetic pulse of up to 2 T (**b**). The pulse has a rise time of about 200 μs and a duration of 1 ms and owing to its intensity and brevity changes at a rapid rate (**c**). The changing magnetic field generates an electric field (**d**) resulting in neural activity or changes in resting potentials (**e**). The net change in charge density in the cortex is zero. The pulse shown here is monophasic, but in studies that require repetitive pulse TMS (rTMS), the waveform will be a train of biphasic pulses which allow repeated stimulation. For an introduction to the details, see REF. 52. (Figure adapted from REF. 95; images of equipment kindly supplied by The Magstim Co. Ltd.)

vision[78] and some aspects of functional specialization of vision[79]. However, in the study of patients with brain damage or monkeys with specific brain lesions, one is studying an abnormal brain. The damaged brain may have undergone months or sometimes years of reorganization and the subject may have acquired a wide repertoire of compensatory strategies to cope with the deficit[80]. As Lomber[81] pithily, but accurately, observes, this "spectre of compensation" means that lesion studies may "examine the capability of other cortical circuits in the absence of the removed cortical tissue and not the true functions of the removed tissue". Because TMS causes a brief, reversible disruption in cortical function it is protected from this spectre and so provides a firmer footing from which to make inferences about the function of the normal brain. The seminal experiments pertaining to the cognitive application of TMS have been reviewed in detail on several occasions[1–5] but some important advances (discussed in the next section) have occurred only within the last two years and provide further examples of the value of TMS in neuropsychology.

Virtual neuropsychology. Although patients may be available, their deficits are often transient. It is here that TMS can be used to formally reproduce the basis of the deficit of interest. For example, Fierro *et al.*[82] applied rTMS (25 Hz for 400 ms) over the right parietal cortex to induce a transient neglect syndrome. Subjects were asked to judge whether a briefly presented line was bisected centrally, or to the left or the right of centre. Patients with right parietal damage and left hemineglect typically underestimated the length of the left side of the line. Normal subjects, without TMS, tend to overestimate the length of the left side of the line (known as a 'pseudoneglect'). Right-sided TMS reduced this pseudoneglect, that is, it caused subjects to underestimate the left side of the line relative to their own normal judgement. Here, then, is a transient, but formal and reproducible recreation of an effect associated with neglect that can be used to test the theories resulting from classical neuropsychological studies. The protocol adopted by Fierro *et al.* might also be more powerful if it could be developed in a reaction-time paradigm, which might allow the application of single pulse TMS and therefore chronometric analysis of the neglect syndrome. This study illustrates how TMS can be used to advance neuropsychology. First, Fierro *et al.* addressed a robust and widely studied phenomenon, the first step in any convincing extensions of neuropsychological findings. Second, they observed a surface difference between the TMS-induced deficits and the deficits seen in patients. This latter point is a feature of many TMS studies and far from driving a wedge between real and virtual neuropsychology, it demands that each approach take note of the differences observed with permanent and transient lesions. From the standpoint of making inferences about normal brain function, a dialogue between the results of these two disciplines is not an optional extra — it is an absolute necessity. The differences between real and virtual lesions may be accounted for by the effects of diaschisis (changes in activity

and function at sites anatomically connected to the lesion) and reorganization over time. The theoretical and perhaps practical consequences of understanding the time course of the effects of diaschisis and reorganization may be considerable[83], and some studies tracking the changes in motor representation following amputation have already proved fruitful in this regard[21].

Dynamic connectivity. TMS can also be used to explore brain function in patients. One of the recent controversies concerning visual awareness is whether the specialized secondary visual areas such as V4 and V5 are sufficient for awareness of their preferred attribute (for example, colour or motion), or whether they must interact with V1 to generate awareness[84,85]. A recent study[28] applied TMS to extrastriate visual area V5 in a patient with almost total destruction of the striate cortex in the left hemisphere. TMS over area V5 can produce the illusory perception of motion in normal individuals[10,86]; the question is whether it can also elicit motion perception in the absence of V1. The patient perceived normal moving phosphenes when V5 was stimulated in the cerebral hemisphere that had an intact V1, but motion perception could not be elicited from the blind hemifield by stimulating the hemisphere without an intact V1. The importance of V1–V5 interactions was further substantiated by the production of moving phosphenes in a peripherally blind patient by stimulation over area V5. This patient had suffered traumatic destruction of the optic nerves, but V1 was intact in both hemispheres[28]. This combination of real and virtual lesions is still in its infancy but it is clearly a paradigm that needs further exploration. Neurophysiological studies have recently recorded the timing of interactions between extrastriate and striate cortex by cooling V5 while recording from V1. The effect of V5 deactivation occurred remarkably early — in the first 10 ms or so of the V1 response[87]. Evidence of similarly fast, or perhaps continuous communication may be observed if TMS can be used to study the dynamics of backprojections in humans. The usual effect of V5 stimulation is to produce a perception of moving phosphenes, but this may be weakened or even abolished if V1 is stimulated within a critical time window of the V5–V1 interaction. This of course would not imply that movement is perceived in V1, only that it is necessary for movement perception.

Language and memory. The effects of TMS on speech are well known and it is now clear that TMS can induce speech disruption that is dissociated from motor effects[25–27]. As far as neuropsychology is concerned, however, this area awaits theoretically driven studies on the basis of psychological theories of language function. There have been demonstrations that applying TMS over the left frontal cortex can not only disrupt speech production but also impair verbal recall[27] and picture–word matching[88]. TMS over the posterior regions of language-related systems can also disrupt[89] or facilitate picture naming[90]. However, with the exception of one study based on neuroimaging data, the drive has been phenomenological rather than theoretical. The time course of verbal memory and recall and many of the different stages of verbal processing remain to be explored by TMS. Studies of memory[5] are also in their infancy, and the combination of psychological techniques for the study of episodic memory or the effects of confidence judgements during recall are other areas awaiting investigation.

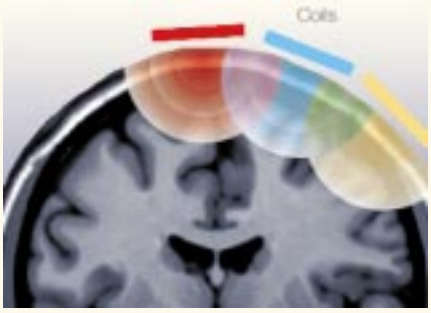


Figure 3 | **Subtractive lesion analysis applied to TMS.** From models of TMS-induced electric fields one can infer the region of stimulation. By stimulating at neighbouring regions on the scalp the inferences can be refined and, notwithstanding the uncertainty of any one field, reasonable functional anatomical attributions can be made. The 'coils' and induced fields in this figure are illustrative of the methodological rationale and do not represent real configurations and effects.

The future of TMS

Metamagnetism. The recent technical achievement of combining TMS with PET and MRI has been useful in studying the connectivity of the human brain, in validating the specificity of TMS and in guiding the location of TMS application. Looking to the future, the next step is to combine TMS, fMRI and PET in behavioural studies. One method that has already been used successfully is the application of low frequency TMS (for example, 1 Hz for 15 minutes) 20 minutes before the subject performs a task in the scanner[9]. Low frequency rTMS reduces blood flow in the region stimulated for several minutes and can also produce a concomitant reduction in behavioural performance of tasks that rely on that area. This 'distal' stimulation method (applying rTMS for several minutes before behavioural testing) can be used to establish a correlation between imaging results and virtual lesion effects, and has been used successfully in studies of visual imagery[9] and depression[36,37]. Direct measures of the effects of TMS during fMRI are more challenging, but Bohning and colleagues[67,68] have already shown that the two techniques can be combined. Indeed, the spatial and temporal resolution of this combination promises to make the TMS/fMRI partnership a valuable one in future years. It should be stressed, however, that the conclusions that can be drawn from TMS are constrained by the necessity for hypotheses about both the temporal and spatial aspects of the function under investigation. The likelihood of obtaining an interpretable behavioural deficit on a particular task by randomly stimulating over the cortex is slight. On this analysis, the ability to test the necessity and sufficiency of a given brain region by application of TMS should provide a further constraint for theories of brain functional localization on the basis of neuroimaging data.

Virtual lesions of real brains. The results from TMS can sometimes challenge those of classical lesion studies[1,17] and this requires a means of assessing the significance of the difference between the results of real and virtual lesions. As mentioned above, diaschisis may cause false inferences to be made in the analysis of lesions. Lesions of neural network models provide a third lesion technique, which may be helpful in guiding the conclusions one can draw from patients or TMS results. Recent studies[91–93] have modelled classical and paradoxical effects of brain lesions and the results from these studies may provide another level of constraint on the interpretation of the

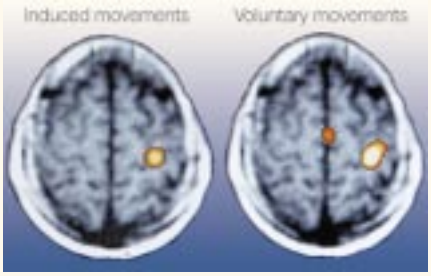


Figure 4 | **Spatial and functional specificity of TMS.** This specificity is evident in the correspondence between blood flow changes induced by TMS over the motor cortex to produce a finger movement, and the activity produced by an intentional movement, which also produces supplementary motor area activity. (Adapted with permission from REF. 66.)

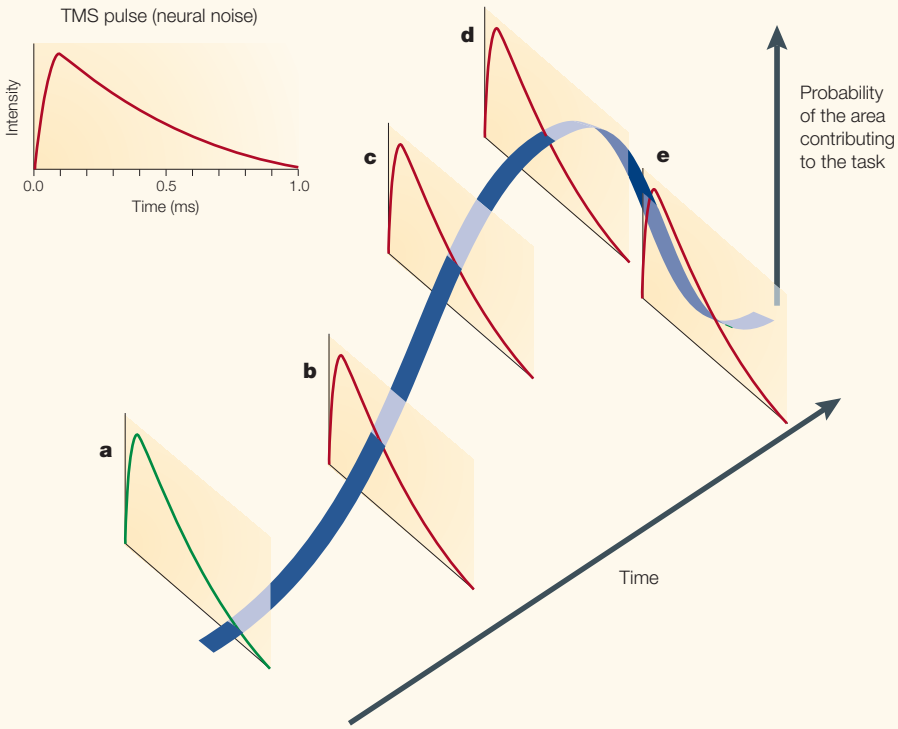


Figure 5 | **Temporal relationship between transcranial magnetic stimulation and behaviour.** A probabilistic picture of the relationship between pulse strength and behavioural effects. The upper panel shows that the intensity of the transcranial magnetic stimulation (TMS) pulse is greatest close to the time of onset and then declines within one millisecond. The effect this has on behaviour is a function of the intensity of the physiological effects of TMS and the probability that the neurons stimulated are critical to the task. **a** | The pulse here would not have a behavioural effect because it is applied too early. **b** | The pulse here would interfere with behaviour because an early (that is, high) phase of the TMS noise is applied even though the probability of the area's involvement is low. **c**,**d** | Similarly, the pulses here would have a behavioural effect because of the high probability of the area's involvement at the time of the pulse. **c**,**e** | Although the pulses applied here arrive at similar parts of the probability curve, the neural noise at **e** is higher because there is no recovery time. So the product of neural noise and neural necessity would be higher at **e** than at **c**. The time course of TMS effects in this framework shows that the temporal resolution of TMS is limited by two factors: duration of TMS pulse effects and duration of an area's involvement in the task. The figure also illustrates why the effect of TMS need not necessarily correspond to the timing of the event-related potentials or magnetoencephalographic signals. The appropriate application of TMS may have effects at times well before **b** and **c** or well after **e**, the reported peak.

effects of TMS. In one simulation, for example, the connectivity of an area was a strong determinant of the effect of the lesions on the rest of the network, as well as of how that area responded to a lesion elsewhere in the system. This may seem an unsurprising statement, but the analysis of lesions does not really take this into account, perhaps because the wide variability in cortical connectivity would add many layers of complexity. Nevertheless, formal models of the probable interactions between areas on the basis of anatomical connectivity may be a rich source of predictions that can be tested with TMS.

Conclusions and cautions. TMS has been used in studies of cognitive and sensory functions for over a decade, although much less extensively than functional neuroimaging by PET or fMRI. Its period of being a 'new and exciting' technique is over and work with TMS must now be judged within the theoretical frameworks used to evaluate other neurocognitive approaches. TMS has clearly made a contribution to the understanding of perception, attention awareness and plasticity. Further progress, however, will depend on the application of TMS in other areas such as the neuropsychology of language and memory. The combination of TMS with other techniques, in conjunction with formal predictions on the basis of lesions of neural networks should provide fruitful avenues of research.

Many procedural and methodological hurdles remain, however, and the reliability and replicability of TMS effects in cognitive studies is a long way from that achieved in neurophysiological studies. The effects of TMS at anatomically connected areas also require careful consideration when developing good control procedures. It is to be hoped that the accumulation of experience from different groups will allow the further development of this method[2]. One possibility for 'fast tracking' the methodological advance of TMS in studies of cognition might be some form of data sharing, as recently suggested for other areas of neuroscience[94]. There are good reasons to approach this with caution, but in some cases, for example, mapping phosphenes on individual MRI scans or comparing the effects of different coils in similar experimental situations, data sharing may lead to faster and more efficient methodological advancement.

Vincent Walsh and Alan Cowey are at the Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford, OX1 3UD, UK.
e-mail: vin@psy.ox.ac.uk

Links

FURTHER INFORMATION

The International Society for Transcranial Stimulation

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