A primer of magnetic stimulation as a tool for neuropsychology

Vincent Walsh*, Matthew Rushworth

Department of Experimental Psychology, University of Oxford, South Parks Rd, Oxford OX1 3UD, UK

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Abstract

Transcranial magnetic stimulation (TMS) offers the neuropsychologist a ‘virtual lesion’ method of investigating the effects of cortical dysfunction. Classical neuropsychology relies on patients with irreversible, and often diffuse brain lesions and these factors place limitations on the inferences that can be drawn about normal brain function. Thus the neuropsychologist is constrained by the extent to which the damaged brain undergoes reorganisation and by the inability to address questions regarding the timing of cognitive functions. TMS can disrupt cognitive functions for a few tens of milliseconds (although some effects of TMS can be seen for longer), with spatial resolution in the order of a centimetre and therefore allows one to study the role of brain areas without the masking effects of cortical reorganisation. The spatial and temporal resolutions are not unique to TMS but because TMS can be used as a temporary interference technique, it has a functional resolution with which one can address questions beyond the range of other neuroimaging and patient studies. Here we outline how TMS produces transitory ‘lesion’ effects, examine how the effects of stimulation spread in depth and breadth across the cortex and discuss the principles of the use of TMS in neuropsychology. Finally, we also itemise some issues of safety.

1. Introduction

If one were to provide a crude list of the goals of cognitive neuropsychology it would probably read something like ‘where? what? and when?’. Neuropsychology, and especially so with the use of PET and fMRI, has been very successful at proposing candidate answers for the ‘where?’ question: one can localise some visual functions to regions of the extrastriate cortex [85], language functions to regions of the temporal and frontal cortices [64] and memory and decision making functions to prefrontal regions [29, 58]—the list could go on. But localisation of function is not the main or even a principal concern of many neuropsychologists and functional dissociations can occur without an appreciable difference between lesions. The ‘what?’ question is more central to neuropsychology: i.e., what are the components of the task being analysed?

To answer this question, neuropsychologists have the problem of making statements about function in the intact brain, inferred from studies of injured brains. Shallice discusses two possible approaches to this question: ‘The first is to make an assumption about the overall structure of the system—say that it is broadly modular in Marr’s sense. One then asks what neuropsychological findings tell us about its detailed functional architecture—... The second approach asks whether neuropsychological findings tell us anything about the types of basic elements out of which cognition might be constructed’ [Ref. 26, p. 21]. Modern experimental psychological theory does not just consider the basic organisation of a system, i.e., its modularity; it also considers the ordering, interaction and evolution through time of the system’s basic elements. Because of its time limited, reversible, and repeatable nature TMS allows neuropsychologists to frame questions about these important issues: the ordering of component processes [15, 71], their interaction [82], and their evolution through time, particularly as a result of learning [31, 81].

Discussion of the technology of modern cognitive neuroscience often centres on questions of spatial and temporal resolution. It can be argued, however, that TMS has a cognitive resolution that distinguishes it as an essential weapon in the neuropsychologist’s contemporary armoury. It is becoming increasingly clear that it is necessary also to consider the functional integration of different brain areas in order to understand how even simple cognitive tasks are performed. It is possible that it is only from the perspective of functional integration that we can understand the role of cortical areas, such as the prefrontal cortex, that lie at some distance from

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*Corresponding author. Tel.: 01865 271326; fax: 01865 310447; e-mail: vincent.walsh@psy.ox.ac.uk.

1 Correspondence can be addressed to Mr M. Rushworth. E-mail: matthew.rushworth@psy.ox.ac.uk.
primary sensory or motor areas. The temporal resolution and reversibility of TMS mean that it is well suited for investigating functional interactions and changes in functional interaction during the course of learning. Other brain mapping techniques record brain activity which is correlated with some behavioural event. But the correlations do not show that an area is necessary for a particular function. TMS, on the other hand, because it is an interference technique, can be used to establish the necessity of a brain region for cognitive processes.

There are some practical limitations to working with patients that preclude the use of experimental techniques that have been fruitful in other areas of psychology; as we shall see, TMS does not suffer from the same limitations. Many psychological studies use reaction time (RT) as the dependent variable and from these inferences can be drawn about the order in which certain functions occur [63, 78], the resources required for each additional processing component added to a task (e.g., the effect of adding more items to a visual search display—[Ref. 80], the cost of switching from one type of stimulus or task to another—[Ref. 1]) or interactions between different elements of processing (e.g., the reversal of performance in visual search—[Ref. 23]). In many patients, brain damage is widespread and may not just affect the cognitive tasks of interest but it may also affect basic processes involved in response production. In such cases it is difficult to obtain reliable and consistent baseline and task-related measures of RT. In cognitive tasks, the limited interference caused by single pulse TMS may be insufficient to cause subjects to make errors but it is compatible with RT paradigms [15, 52, 67].

Practical considerations can also make it difficult to carry out psychophysical experiments with neuropsychological patients; again the designs can be too subtle and too demanding to be profitably used with a patient who has suffered brain damage. Nevertheless, if one wishes to make statements about the fundamental elements of processing it is often necessary to do so by probing only the most sensitive of mechanisms, i.e., those working at the limits of detection, discrimination or decision making. It is already clear that TMS can be successfully combined with psychophysical methods [43, 50].

2. How does TMS work?

During transcranial magnetic stimulation a brief magnetic pulse is applied over the scalp of a subject, at a point which overlies a specific cortical area. The pulse is generated from a number of capacitors which discharge a large brief current into a coil held above the subject’s head. The current generates a magnetic field below the coil and this field passes, unattenuated by the skin and scalp, into the cortex. The effect of the magnetic field at the cortex is to induce a current which results in neural activity. Figure 1 shows the cycle of events in a single pulse stimulation. The important points here are that a large current (8 kA in the example shown) is required to generate a magnetic field of sufficient intensity to stimulate the cortex and that the electric field induced in the cortex is dependent upon the rate of change as well as the intensity of the magnetic field. To achieve this latter requirement the current is delivered to the coil with a very short rise time (approx. 200 us) and the pulse has an overall duration of approximately one millisecond. The induced field has two sources [68]. One is the induction effect from the current in the coil (and this is what is usually meant when discussing TMS); the other is an accumulation of charge on the scalp or between the scalp and the skull.

Magnetic stimulation can be applied either in single pulse or repetitive pulse mode (rTMS). In single pulse mode the stimulation is delivered at a precise point in time during a task. In multi pulse mode a repeated train of pulses can be applied at rates of up to 50 Hz and for durations of tens, hundreds or thousands of ms. Experimentally they differ in that rTMS is useful for localising brain regions but does not possess the temporal resolution of single pulse TMS. There is also some indication that whereas single pulse TMS can cause subjects to produce errors on sensory detection tasks it is far less successful at doing so in more cognitive tasks. For this reason the study of language [12] and memory [30] is usually carried out with rTMS. However, as we discuss below, there is a role for single pulse TMS in the study of cognition when dependent variables other than error rates are measured.

Many TMS studies have explored the effect that TMS has on peripheral measures such as EMG recordings taken from various muscles [51, 68]. It soon became clear, however, that such peripheral EMG phenomena are the consequence of an interaction with central, cortical processing [17, 33, 34]. This was graphically illustrated in an experiment reported by Lemon et al. [47] in which TMS pulses directed at the motor cortex were delivered at different stages of reaching movements. The TMS effect on EMG depended on the time of the pulse’s delivery. The most critical times, however, did not correspond to the times of greatest background muscular activity. Similar task related changes in vulnerability to motor cortical TMS have been recorded directly in the bulbular pyramid of the macaque, upstream of the spinal cord and muscles [6]. It seems likely, then, that TMS is most effective when it coincides with a critical epoch of cortical processing. In the macaque, the latencies of lumbar sacral axonal responses to scalp TMS are consistent with a cortical site of action [24]. In human subjects, PET has been used to demonstrate an increase in cortical synaptic activity, as indexed by increased regional cerebral blood flow (rCBF), in the cortex below the point of stimulation [61, 62]. Many of the effects of TMS are
Fig. 1. Sequence of events in TMS: delivery of a single pulse. An electrical current of up to 8 kA is generated by a capacitor and discharged (top panel) into a circular, or figure-of-eight shaped, coil which in turn produces a magnetic pulse of up to 2 Tesla. The pulse has a rise time of approximately 200 us and a duration of 1 ms (2nd panel) and due to its intensity and brevity changes at a rapid rate (panel 3). The changing magnetic field generates an electric field (panel 4), resulting in neural activity (panel 5). The net change in charge density in the cortex is zero (panel 6). In addition to single pulse stimulation some simulators can deliver trains of pulses up to a rate of 50 Hz. Rapid rate stimulation can induce seizures so there is a trade-off between stimulus intensity and the rate of repetition. The exact area stimulated by the pulse and the depth of stimulation depend on several factors including coil shape and whether the pulse is monophasic or biphasic. The details of the electric current in the stimulating coil and the subsequent effects on neural tissue are taken from Ref. [40] (with permission of The MagStim Company) and are calculated for the MagStim 200 with a 70 mm circular coil.

The effects of TMS are not necessarily excitatory. For example, subthreshold stimulation, which does not affect EMG, can inhibit the effect of subsequent suprathreshold stimulation [46]. Again the inhibitory effect of TMS appears to have a cortical origin; it has no measurable effect in the cervical cord [20], it has no effect on spinal H reflexes [46], but it is affected by cortical myoclonus [65]. Such inhibitory subthreshold stimuli are associated with a decrease in cortical synaptic activity, as indexed by rCBF decreases [60, 62]. TMS applied to a single area can have either a positive or a negative effect depending on the rate of stimulation. Tarazona et al. [79] applied rTMS to the motor cortex at either 1 or 10 Hz while subjects were learning a motor sequence reaction time task. Remarkably, the 1 Hz stimulation, which also decreased cortical activity, was correlated with a slight decrease in implicit learning, but the 10 Hz stimulation, which increased cortical excitability, was correlated with an increase in implicit learning.

Few cognitive studies have exploited the distinct facilitatory and inhibitory effects of TMS. Facilitatory effects have mainly been limited to the production of phosphenes or specific muscle contractions but it is of more psychological interest, for the present, that TMS disrupts the normal pattern of cortical processing. The pulse is applied to the cortex during performance of a task and the intention is not to produce a particular movement or perception, but to delay or worsen performance of the task at hand. In the context of a task the induced current operates as ‘neural noise’, that is, the pulse adds random activity in the midst of organised activity in the cortical region. This neural noise serves to delay or disrupt performance and it is in this sense that TMS operates as a lesion. There is of course no damage to the cortex and no long term effect of the pulse (see Safety, below). There are other uses too of TMS and, for the sake of completeness, Table 1 shows the variety of dependent variables which can be used in TMS, but for the rest of this article, when we refer to TMS, unless qualified, we mean TMS in its disruptive, or lesion mode.

3. Spatial and temporal resolution

The spatial resolution of TMS is, perhaps, not established as firmly as that in imaging techniques such as PET and fMRI. Often, of course, analysis methods and the averaging of several subjects’ data mean that imaging experiments do not, in practice, yield results at the limits of the possible spatial resolution. A full understanding of the relationship between the extent of induced current and the anatomical specificity of effects awaits clarification. However, studies now routinely report the ability of TMS to distinguish the effects of stimulating
Table 1
An outline and examples of the kinds of experimental questions that can be asked with TMS

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Example</th>
<th>References</th>
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<tbody>
<tr>
<td>Muscle activity</td>
<td>(1) In both young monkeys and humans there is a drop in the threshold effect of TMS over motor cortex that is correlated with the development of fine finger movements</td>
<td>[27]</td>
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<td></td>
<td>(2) Changes in size/threshold of the motor cortical representations of muscles during motor skill acquisition</td>
<td>[31]</td>
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<td></td>
<td>(3) The electromyographic effect of TMS over the motor cortex is modulated by motor imagery</td>
<td>[26]</td>
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<tr>
<td></td>
<td>(2) Disruptive: reports of perceptual effects during task performance</td>
<td>[35, 36]</td>
</tr>
<tr>
<td>Assessed self report</td>
<td>Depression studies</td>
<td>[28]</td>
</tr>
<tr>
<td>Behavioural measures</td>
<td>(1) Facilitatory: 10 Hz stimulation of motor cortex enhances implicit learning of a motor sequence</td>
<td>[79]</td>
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<tr>
<td></td>
<td>(2) Interhemispheric facilitation: parietal stimulation increases ipsilateral tactile sensitivity</td>
<td>[75]</td>
</tr>
<tr>
<td></td>
<td>(3) Disruptive: reaction time or error increases during task performance</td>
<td>[7, 31, 38, 52]</td>
</tr>
<tr>
<td>Blood flow and brain activity</td>
<td>Correlations between brain activity and TMS</td>
<td>[37, 60, 61]</td>
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sculpt sites 1.5 cm [71] or 1 cm apart [9]. In a study of the latency and variability of motor evoked potentials (MEPs) recorded in four different muscles, Brasil-Neto et al. [9] were able to distinguish between the effects of TMS on scalp positions 0.5–1 cm apart. These levels of resolution are of course much finer than one could hope to obtain in neuropsychological studies.

The current induced by TMS spreads beyond the intended cortical target area. With transcranial electrical stimulation (TES) of sufficient intensity it is possible to directly stimulate axons at a depth of several tens of ms below the motor cortex [24]. Such direct or D responses are also produced with TMS [4, 24, 59]. At the threshold for their production, however, TMS direct responses appear to be generated near to the cell soma, at the axonal hillock. At such threshold levels intracortically mediated, indirect or I responses predominate [4, 24, 33, 59]. At high levels of stimulation, it is possible that the effect of TMS is partly due to the direct stimulation of axons rather than overlying cortex (e.g., [Ref. 71]).

To enhance the spatial specificity of TMS, figure-of-eight coils are available; but even with these coils the changes in activity in the underlying cortex can spread across several centimetres [48]. Ilmoniemi et al. [37] measured EEG responses after applying TMS to the visual or motor cortex and found that the resulting changes in activity were maximal close to the point of stimulation but also that the effect spread to adjacent areas within 5–10 ms. It is also clear that TMS can elicit activity in distant areas that are anatomically interconnected with the target region [16]. Ilmoniemi et al. [37] found that within about 20 ms of stimulation, EEG effects had spread across the callosum to the homotopic regions of cortex in the contralateral hemisphere (Fig. 2). Paus et al. [61, 62] used PET to analyse the anatomical distribution of the effects of TMS applied to the frontal eye fields. The result was not only an increase in rCBF at the stimulated site, but also at several sites anatomically connected to the frontal eye fields. The message here is clear. TMS does stimulate cortical areas but the effect is not limited to the site at which the pulse is directed. This has implications for the choice of control conditions, discussed below.

It is difficult to estimate the length of time for which a single TMS pulse interferes with cortical processing. Suprathreshold TMS can delay movements for up to 150 ms [18], but not all of the delay is due to the pulse’s effect on the cortex. The inhibitory or conditioning effect of subthreshold TMS pulses on subsequent suprathreshold TMS pulses is maximal when the inter-pulse interval is less than just 6 ms [46]. Pulses between 1.3–1.9 Tesla intensity have an effect on scalp EEG at any given position for a time period somewhere between 20–30 ms [37]. Schluter et al. [71] compared the effect of TMS over three different sites in the region of the motor and the dorsal premotor (PMd) cortices. TMS over the most anterior site disrupted performance when it was delivered 140 ms after the presentation of the cue for movement. TMS at an adjacent site 1.5 cm away was most effective when it was delivered 40 ms later.

The critical time for TMS delivery to a human brain area appears to coincide with the time at which single unit responses can first be recorded from the homologous area of the macaque brain. For example, the critical period for human PMd TMS, at 140 ms [71], corresponds to a time when more than 20% of macaque PMd neurons have begun to respond in a movement selection task [21]. The critical time periods for TMS applied to V1 [15] are also comparable with macaque single unit data.

Some aspects of the critical time periods for TMS...
appear anomalous. In some cases the critical periods are earlier than would be expected on the basis of human scalp recorded event related potentials (ERPs). This may be because ERPs only become recordable when large populations of neurons are synchronously active and ERP data usually refer to the point at which maximum task-related activity is recorded. Whether TMS yields a more accurate estimation of the time course of events remains to be explored but the indications to date are that TMS timing data are closer to estimates based on studies of single unit recordings [5, 15, 21].

The brevity of the critical period of TMS also needs to be explained. For example, the distinct 40 ms period during which human PMd, but not primary motor cortex, is vulnerable to TMS is difficult to reconcile with the data from the macaque that suggest that many cells in both areas are concurrently active for a longer period of time [41, 42, 73, 74]. The same single unit studies suggest that there is a limited period when just the PMd cells may be encoding a task parameter. It may be the case that a cortical area is only vulnerable to TMS during the time period that the area uniquely codes for a certain aspect of task performance [15].

4. Necessary and sufficient control conditions

Clearly, it is not enough to stimulate a region and observe an effect; one has to be sure that the effects are either specific in time or in space or to the particular task used. In neuropsychological or primate lesion studies the specificity of the deficits reported are ensured by control tasks, in which a lesion affects task A but not task B, or by lesion controls, in which lesion X affects task A but lesion Y does not, or both—lesion X affects task A but not B and lesion Y affects task B but not A. All these approaches are valid in TMS experiments. The choice of control site can be determined in one of three ways that we shall call dissociation, proximity, and time. The dissociation method is of course already familiar to neu-
ropropsychology—one simply selects two areas posited to have different functions and applies TMS to the two using exactly the same logic as one would in a lesion study using non-human primates (see [Ref. 53]). For an example of proximity, suppose one wished to examine the effects of parietal cortex stimulation on an eye movement task. It would be reasonable to stimulate a grid of points during the task centred on, say, the P4 electrode site and compare the site at which an effect was obtained with those surrounding points at which TMS had no effect (see e.g., [Ref. 54]). The proximity method results in a statement to the effect that ‘area X is important for task A but neighbouring sites are not’. The proximity method is particularly important where structural MRI scans of individual subjects are not available to help localise areas of cortex and it is also useful in pilot experiments. It may also appeal to those for whom the anatomy is of secondary importance to the business of obtaining informative functional dissociations. The early work of Amassian for example is uninformative with respect to the localisation of TMS effects, but the stimulus and task specificity of the effects of TMS helped to lay the foundations for current experiments on visual perception [3].

Among interference techniques, dissociations in time are unique to TMS. A number of studies have contrasted the time at which TMS has an effect at two brain areas [8, 15, 71]. TMS can of course be used to assess the role of functional areas at much longer time scales. A recent TMS study has exploited this aspect of TMS to investigate functional plasticity over periods of several minutes. Classen et al. [11] measured TMS-evoked responses to stimulation of the cortical representation of the thumb. The direction of the elicited thumb movement was consistent as shown in Fig. 3. Subjects were then given a simple motor skill learning task (directed thumb movements in a direction opposite to the direction of TMS-evoked thumb movements). TMS was used after training, again to evoke directionally selective thumb movements. As a result of training, cortical stimulation now elicited thumb movements in the trained direction, indicating that the organisation of thumb representation underwent learning-related changes. To produce this effect training took place over periods between 5–30 min. The direction of thumb movements elicited by TMS after training was monitored to assess the time required for the thumb representation to return to normal. As Fig. 3 shows, 20 min after training the TMS-evoked movements were predominantly in the trained direction.

Other studies of plasticity have demonstrated cortical changes occurring over minutes [86], hours, months and years [13, 14, 32, 45, 56, 81]. For example, Pascual-Leone and Torres measured the extent to which the cortical representation of the Braille reading fingers were expanded relative to non-Braille reading fingers. Somatosensory evoked potentials were significantly larger when recorded from stimulation of the representation of the Braille fingers than the non-Braille fingers and the representation of the Braille fingers was also shown to be expanded by 2–3 times in area.

The peripheral effects of TMS also need to be considered. The delivery of a magnetic pulse produces a sharp audible crack and it is important to be sure that this is not a distracting stimulus which could impair performance. TMS applied to the scalp is also likely to stimulate facial muscles and so produce face twitches or eye blinks. A simple control for eye blink artefacts is to run trials in which eye blinks are caused by stimulation of the seventh cranial nerve. Face twitches are likely to be produced by stimulation at some of the control sites mentioned above.

5. Paradoxical lesions

Brain lesions can sometimes produce improvements in some kinds of performance. These effects are not as common as the deleterious consequences but they can be equally informative. Sprague [77], for example, excised the entire visual cortex from one hemisphere of the cat and observed, as one would expect, a contralateral hemianopia. However, removal of the superior colliculus contralateral to the cortical lesion could restore some visual orienting abilities. Another example of paradoxical facilitation is the improvement in tactile sensitivity in the hand ipsilateral to a parietal lobe lesion ([75]; see Kapur [44] for review). One reason for the difficulty in investigating improvements in neuropsychological patients may be that as the patient learns to use a damaged brain system to deal with the world, reorganisation and new strategies cause any benefits of the damage to be masked. The disorganisation caused by TMS, however, is likely to be too short for the brain to begin to reorganise and behavioural facilitations are something which can be studied intentionally rather than serendipitously.

Perhaps ‘paradoxical’ is no longer the correct term for these kinds of findings and it may be better to consider them as revealing competing and mutually inhibitory systems in the brain. In the visual system, for example, TMS over area V5 impairs performance on a visual search task which requires attention to motion but speeds up performance on a search task that requires attention to form and colour [82]. A reasonable hypothesis to generate from this finding is that areas necessary for colour and motion perception compete for processing resources in much the same way as stimuli are considered to compete in some models of visual attention [19].

6. Safety ‘beware of an optimist wielding a stimulating coil’ [Ref. 40]

The use of TMS is rightly subject to approval by local ethical committees and there are some precautions which
Fig. 3. The effects of training on cortical representation from Classen et al. [11]. TMS was used to evoke thumb movements (A) before training. Subjects were then given a training task in which movements were made in the direction opposite to that evoked by TMS. After a few minutes training, TMS applied to the same scalp location as before training, elicited thumb movements in the trained rather than the pretrained direction. The bottom trace shows that after training was completed there was a gradual return to the pretraining response to stimulation of motor cortex. Reproduced with the permission of the authors and the American Physiological Society.

must be taken in all studies using the technique. The safety of single pulse stimulation is well established but further precautions should be taken when using repetitive-pulse TMS. Repetitive-pulse TMS can cause seizures.

The magnetic field produced by stimulating coils can cause a loud noise and temporary elevations in auditory thresholds have been reported [57]. The use of ear plugs is recommended in all experiments. Some subjects may experience headaches or nausea or may simply find the face twitches and other peripheral effects of TMS too uncomfortable. Such subjects obviously should be released from any obligation to continue the experiments. More serious are the concerns that TMS may induce an epileptic seizure. There are a number of cases of epileptic fits induced by repetitive pulse TMS and caution is necessary. As a guide, any subject with any personal or family history of epilepsy or other neurological condition should be precluded from partaking in an experiment which does not involve investigation of that condition. Pascual-Leone et al. [57] assessed the safety of rTMS and noted that seizures could be induced in subjects who were not associated with any risk factors. The paper presents some guidelines for the use of rTMS and familiarity with this paper should be a prerequisite of using rTMS. The paper is only one guide and it is not exhaustive. Further, the study deals only with three sites of stimulation and expresses pulse intensity as a percentage of motor threshold. Studies which apply rTMS to the prefrontal or occipital visual areas cannot merely lift criteria from this paper and assume they transfer to other conditions. We also recommend that anyone wishing to use rTMS visit the TMS website (http://pni.unibe.ch/mailinglist.htm). The TMS community is constantly reviewing safety procedures and this website is a starting point for access to sound information.

A more recent paper [83] summarizes the consensus that exists within the community. The adverse effects recorded include seizures (though these are rare), some enhancement effects on motor reaction time and verbal recall, and effects on affect (some subjects have been reported to cry following left prefrontal rTMS, and others to laugh). There is little information about potential longer term problems with rTMS but the issue cannot be ducked. If, on the one hand rTMS is potentially useful in the alleviation of depression [28] it must be conceded that rTMS can have longer term effects. It would be disingenuous to suggest that all long term effects are likely to be beneficial rather than deleterious. It should be
Fig. 4. Applying TMS to a region of cortex can enhance or inhibit performance on different tasks. The top figure shows six visual search tasks in which subjects were required to detect the presence absence of a target. The figure below shows the effects of applying TMS to area V4. In two tasks (tasks a and b) there is little or no effect of TMS. When TMS is applied to V5 during a search requiring attention to motion (tasks e and f) performance is significantly slower with TMS. Tasks on which attention to attributes other than motion is required are facilitated by TMS over V5. The dotted line at 1 represents reaction times without TMS. Solid lines show reaction times with TMS relative to without. From [Ref. 71].

noted, however, that the improvements in mood as a result of rTMS follow several sessions of magnetic stimulation and that the effects may be cumulative [28]. A simple precaution that may be taken is to prevent individual subjects from taking part in repeated experiments over a short period of time.
As with the paper by Pascual-Leone et al., [57] the use of rTMS should follow a close reading of Wassermann’s [83] report.

References


