Studies in Cognition: The Problems Solved and Created by Transcranial Magnetic Stimulation

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Abstract

■ The application of transcranial magnetic stimulation (TMS) to investigate important questions in cognitive neuroscience has increased considerably in the last few years. TMS can provide substantial insights into the nature and the chronometry of the computations performed by specific cortical areas during various aspects of cognition. However, the use of TMS in cognitive studies has many potential perils and pitfalls. Although TMS can help bridge the gap between psychological models and brain-based arguments of cognitive functions, hypothesis-driven carefully designed experiments that acknowledge the current limitations of TMS are critical. ■

INTRODUCTION

A Problem Found

The history of science reveals a recurring pattern of technological advance preceding and supporting a period of scientific inquiry (Crump, 2001). This concept can be applied to the science of cognition, currently dominated by techniques relying upon secondary measures of brain activity and implicating rather than demonstrating the critical contribution of a brain area to behavior. Most neuroimaging methods ''correlate,'' with varying degrees of spatial and temporal accuracy, a network of brain areas to a cognitive task. This is true of techniques that use reasonably direct measures of brain activity, such as event-related potentials, and of those that rely on less direct measures such as blood flow or oxygen consumption—for example, functional magnetic resonance imaging. Consequently, despite elegant and ingenious experimental designs, these methods offer little or no insight into whether a brain region has a pivotal or merely subsidiary role in shaping behavior.

The interpretative problems of many functional imaging studies can be even greater because brain areas making a critical contribution may show no discernible change in activity during a task. This problem of false negatives contributed to the widespread notion that the prefrontal cortex had a limited role in sequence learning (Clegg, DiGirolamo, & Keele, 1998). A subject can learn a sequence of finger movements with and without awareness for the underlying pattern. A variety of behavioral and imaging paradigms have sought to map these different types of sequence learning onto distinct neuronal circuits (e.g., Grafton, Hazeltine, & Ivry, 1995). Generally, these studies showed recruitment of the prefrontal cortex *only* when awareness for the sequence had been achieved, leading to the concept that the prefrontal cortex made no contribution to sequence learning except when awareness had developed (Clegg et al., 1998). However, studies with transcranial magnetic stimulation (TMS) and on patients with focal lesions suggest a critical role for the prefrontal cortex even in the absence of awareness (Robertson, Tormos, Maeda, & Pascual-Leone, 2001; Gomez-Beldarrain, Grafman, Pascual-Leone, & Garcia-Monco, 1999; Pascual-Leone, Wassermann, Grafman, & Hallett, 1996). This discrepancy between imaging and disruptive experiments appears to have now been clarified thanks to an elegant imaging study; showing that the prefrontal cortex is recruited during all types of sequence learning (Willingham, Salidis, & Gabrieli, 2002). This example illustrates how major shortcomings of one technique, in this case, the false negatives of functional imaging, can be overcome by the application of a complementary technique such as TMS (Fitzpatrick & Rothman, 2002). Traditionally, the interpretative gap between correlation and causation has been bridged by carefully observing the behavioral consequences of focal brain damage in patients. However, the relationship between a behavioral impairment and the site of damage is at best uncertain. Behavioral changes following an insult reflect the capacity of the rest of the brain to compensate (Kolb & Wishaw, 1998). Hence, no simple relationship can be implied between a brain area and an aspect of behavior. In addition, the inherent plasticity of the brain causes behavioral impairments to evolve through time. Such change is the product of a complex interplay between properties of the brain and the natural history of the

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disease. Furthermore, damage is seldom well demarcated or completely isolated and its location often reflects the vagaries of the cerebrovascular system rather than conforming neatly to the needs of the cognitive scientist. The fog surrounding these interpretative dilemmas becomes even thicker with the effects of long-standing medications.

An ability to directly inquire about the causal contribution of different brain areas to behavior is greatly needed. Recent years have seen this need partly assuaged by TMS (Walsh & Pascual-Leone, 2003).

A Problem Lost

Moving beyond a merely correlative description of the relationship between brain and behavior is the fresh approach offered by TMS. It allows the noninvasive electromagnetic stimulation of cortical sites. This principle was demonstrated almost 20 years ago with involuntary finger movement elicited by stimulation over the motor cortex (Barker, Jalinous, & Freeston, 1985). The magnetic field produced around a coil can pass readily across the scalp and skull and induces an electrical current within the brain tissue. This occurs with minimal attenuation of the magnetic field. Consequently, significant currents can be induced without having to apply substantial voltages across the skull, minimizing the activation of pain fibers. Early studies used single-pulse TMS to the occipital cortex time-locked to the presentation of a visual stimulus to induce errors in the detection of letters (Amassian et al., 1989). These errors were maximal with TMS applied between 80 and 100 msec following the presentation of the visual stimulus, implying that only at these times was the occipital cortex making a critical contribution to letter recognition (Figure 1). Similar approaches were employed to study the role of the motor cortex in finger movements (Day et al., 1989) and of the somatosensory cortex in tactile perception (Cohen et al., 1997).

This type of experiment can provide insight into *when* a given brain area is making a critical contribution to a behavior. In addition, by applying single TMS pulses separated by a variable interstimulus interval to two different brain areas, the technique can be expanded to improve our understanding of the dynamic interaction between brain areas. This double-pulse paradigm has been successfully applied to explore the role of back-projections in visual awareness (Figure 1; Pascual-Leone & Walsh, 2001).

One major limitation of these single- or paired-pulse TMS paradigms is that there is often insufficient information about the time at which an area makes a critical contribution to a given behavior. TMS needs to be delivered correctly in time *and* space for the very transient disruption of brain function induced by single-pulse TMS to have a measurable behavioral effect. Therefore, the possibility of covering a larger time window with repetitive TMS (rTMS) to first explore the ''space'' dimension has some utility. rTMS allows the site of stimulation to be established while later single-pulse experiments can give insight into the chronometry of this critical contribution to behavior (e.g., the role of the occipital cortex during Braille reading, Figure 2). The combined use of functional neuroimaging to provide spatial information evoked potentials to provide chronometric information, and

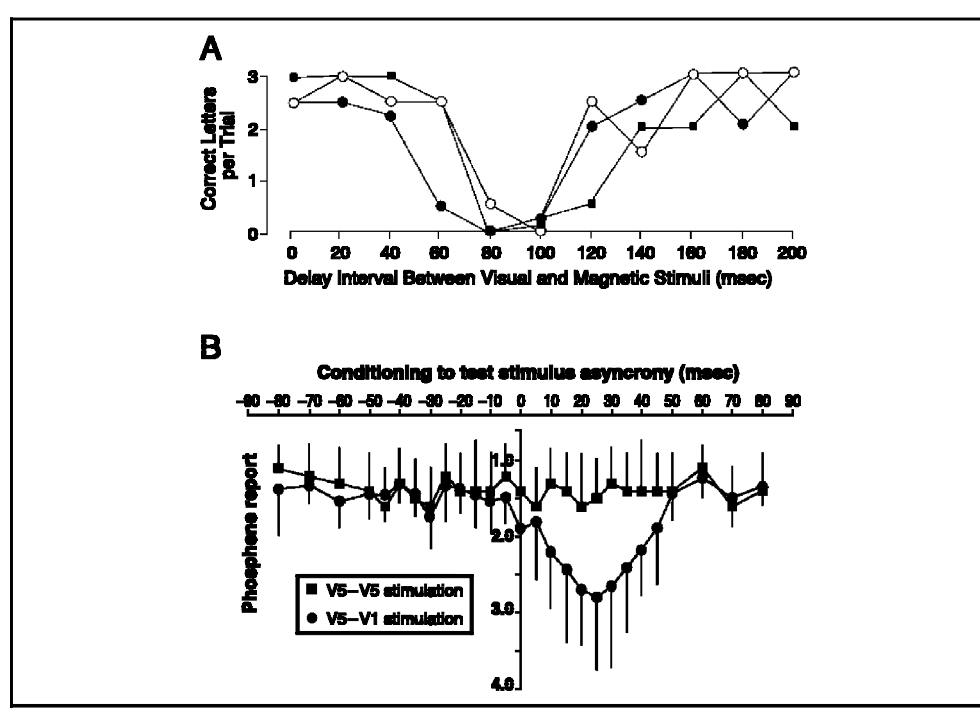

Figure 1. Probing chronometry with TMS. (A) A TMS pulse to the occipital probe can suppress visual perception when it is applied between 80 and 120 msec after stimulus presentation (from Cracco, Maccabee, & Amassian, 1999). (B) The perception of a TMS-induced moving phosphene after stimulation of motion area V5 can be significantly suppressed by a second TMS pulse applied to the primary visual cortex (V1) 10 to 40 msec later. These data show that fast V5–V1 feedback projections are necessary for awareness of motion (from Pascual-Leone & Walsh, 2001).

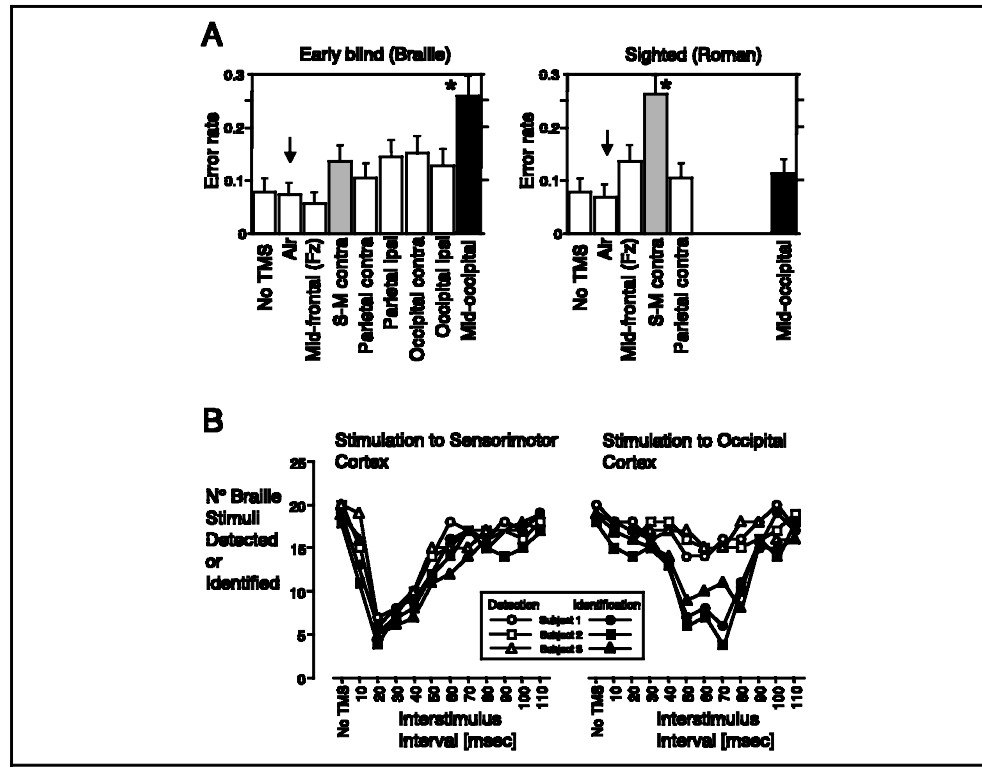

Figure 2. Repetitive versus single-pulse TMS in the establishment of causality and its timing. (A) Short trains of repetitive TMS (10 Hz, 3 sec) to occipital cortex disrupted tactile perception in early blind subjects (EB_B) but not in sighted volunteers (SV_R, Cohen et al., 1997). (B) Later it was shown that in blind subjects TMS to the sensorimotor cortex significantly reduces tactile detection when it is applied 20 msec after stimulus presentation, whereas TMS to the occipital cortex impairs tactile identification when it is applied 60 msec after stimulus presentation (Hamilton & Pascual-Leone, 1998). These studies illustrate that rTMS can reveal those areas making a critical contribution to an aspect of cognition, whereas single pulse allows the time at which this contribution is made to be determined.

TMS to address causality may become a powerful future strategy.

However, as with any experimental technique, TMS it is not without problems. Here we try to explore some of these pitfalls and along the way, point out what has and what can be achieved with TMS in cognitive studies.

Discomfort and Distraction

TMS is commonly described as a ''relatively painless method'' of stimulating the brain noninvasively. Nonetheless, TMS causes significant sensory sensation that can nonspecifically interfere with task performance. This starts with the loud clicking sound as the stimulator is discharged, and continues with stimulation of cranial nerves and the direct activation of facial and neck musculature. These effects are particularly prominent when TMS targets the frontal, temporal, and occipital regions (i.e., the brain areas most commonly targeted in cognitive studies). Several approaches can be used to try to ensure that changes in performance are attributable specifically to the effects that TMS has upon the brain.

Control Sites and Control Tasks

One approach is to stimulate at several sites: If the effects of stimulation are observed exclusively at one site, then this gives some reassurance that the differences across sites are due to the specific effects of neuronal disruption. This comparison across sites assumes that the nonspecific effects of TMS are equivalent. However, even relatively small changes in position can cause substantial changes in the sensory effects of stimulation. Consequently, many studies have also taken the approach of observing behavior across several distinct tasks following stimulation at one site (e.g., Beckers & Zeki, 1995).

Sham Stimulation

An alternative strategy is to use sham stimulation. In this case, although the stimulator discharges giving an audible clicking sound, the magnetic pulse does not traverse across the skull. This is achieved by using specially designed sham stimulation coils, or tilting the coil away from the scalp. The latter is certainly a less desirable alternative and, in some instances, may in fact have a similar effect on the brain as real TMS (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001). However, currently available sham coils need to be improved because they fail to truly mimic the peripheral sensations associated with TMS. Without these sensations, it easily becomes obvious to all but the most naïve subject that they are only receiving sham stimulation.

Timing

A further approach to give experimental control, which can only be used with single-pulse TMS or short trains of ''on-line'' rTMS, is to vary the delay between a particular event (e.g., the presentation of a stimulus) and stimulation. The assumption is that nonspecific distracting

effects of TMS will be independent, whereas the behavioral effects will be highly dependent on the precise interval between the event and the stimulation. This assumption may not be valid in all circumstances. When a stimulus and a pulse are delivered simultaneously, the distraction may be greater than when there is an interval between the stimulus and the TMS pulse. An elegant example of this approach is the disruption caused to the co-ordination between saccadic eye movements and those of the hand at a specific time following saccade onset (van Donkelaar, Less, & Drew, 2000).

''OFF-LINE'' rTMS

A dramatic finding from the early studies using rTMS was the arrest of speech with high-frequency stimulation (Pascual-Leone, Gates, & Dhuna, 1991). Later studies used a similar design, applying high-frequency stimulation while performing a task. This is the so-called on-line paradigm, where both stimulation and task performance occur concurrently (Figure 3). Presumably, the higher the rTMS frequency, the greater the disruption of the targeted brain region, and the greater the behavioral effects. However, the greater the potential risks and the more prominent the nonspecific behavioral and attentional effects can make results difficult to interpret (Wassermann, 1998).

An exciting approach, which has achieved some popularity over the last few years, is to stimulate at a site of interest for 5 to 10 min at 1 Hz, ''before'' starting a cognitive task (Figure 3, Table 1). This ''off-line'' stimulation elegantly removes many of the nonspecific concurrent effects of TMS. Applied initially to investigate visual imagery, this technique has since been used across a variety of cognitive tasks (Walsh & Cowey, 2000; Kosslyn et al., 1999). These studies have consistently demonstrated that the specific effects of rTMS upon behavior and presumably cognition outlast the initial block of stimulation (Table 1). The neurophysiologic bases for these long-lasting disruptive effects are uncertain. Reflecting this uncertainty are the many questions regarding the rTMS parameters necessary to achieve a desired modulation of cortical activity.

TMS PARAMETERS: WHEN AND HOW TO STIMULATE

Selecting the frequency, intensity, and duration of stimulation are difficult and often arbitrary decisions; unfortunately, these can often determine the success or failure of a study. Until more objective ways of selecting parameters become available, a pragmatic and adaptable approach should be taken. The following paragraphs explore some of the pertinent issues surrounding the selection of TMS parameters.

Intensity of Stimulation

Determining the intensity of stimulation required to test a hypothesis (i.e., interfere with a particular function at a specific site) is a substantial problem. At least two factors influence the susceptibility of a brain area to stimulation: magnetic field strength and excitability of the cortex. The strength of the magnetic field produced by a coil decreases exponentially with distance. Hence, the depth traveled from the center of the coil to the cortex largely determines the magnitude of the magnetic field to which

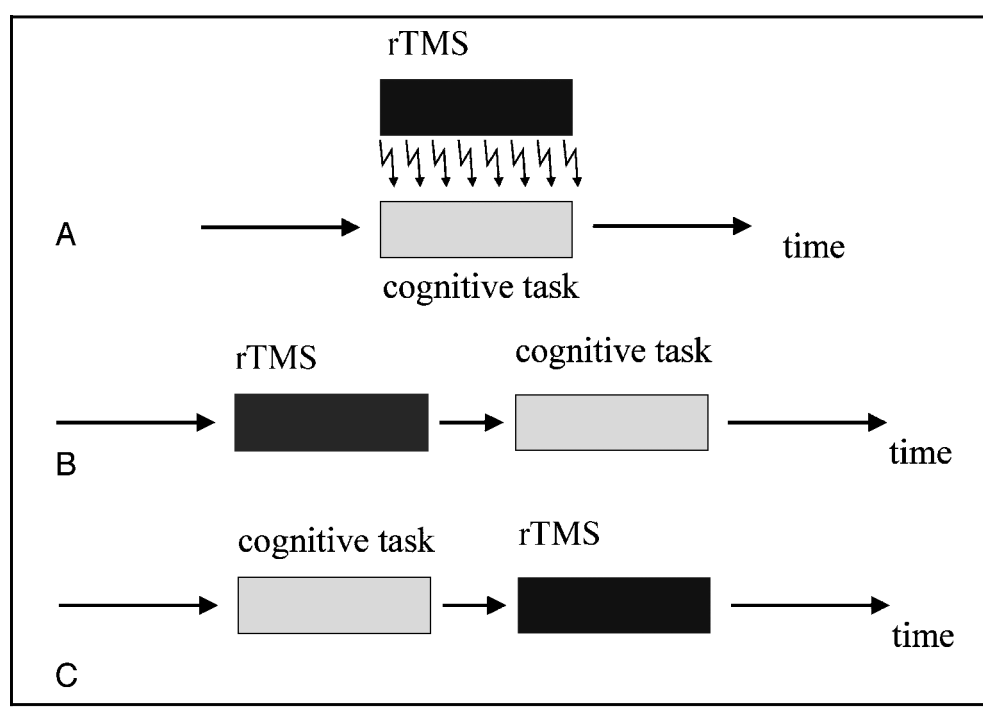

Figure 3. Applying rTMS while performing a task, so-called on-line stimulation (A), has been a widely used approach, yet it suffers from the potential that the nonspecific effects of concurrent stimulation can adversely affect performance. Consequently, recent years have seen the emergence of an ''off-line'' paradigm (B) in which stimulation and performance are dissociated. A new variant of this paradigm, in which a behavior precedes stimulation (C), has very recently been used to study the cortical areas involved in consolidation of motor memories (Muellbacher et al., 2002).

Table 1. Studies that Have Used an ''Off-Line'' Paradigm to Investigate Particular Aspects of Cognition

Authors	*Domain*	*Area*	*Frequency (Hz)*	*Train Duration (min)*	*Intensity*	*Effect Duration*
Kosslyn et al., 1999	Visual imagery/ perception	Area 17	1	10	90% MT	N/A
d'Alfonso, van Honk, Hermans, Postma, & de Haan, 2000	Attention to angry faces	PFC	0.6	15	130% MT	At least 10 min
Hilgetag et al., 2001	Spatial attention	PPC	1	10	90% MT	At least 5 min
Robertson et al., 2001	Motor learning	DLPFC and PPC	1	5	115 % MT	At least 5 min
Théoret, Haque, & Pascual-Leone, 2001	Paced finger tapping	Cerebellum	1	5	90% MT	At least 5 min
Lewald et al., 2002	Spatial hearing	PPC	1	10	60% stim. output	≈11 min
Mottaghy et al., 2002	Visual working memory	DLPFC, DMPFC, VPFC	1	10	90% MT	≈5 min
Sack et al., 2002	Visuospatial functions	Parietal	1	10	80% MT	N/A
Shapiro, Pascual-Leone, Mottaghy, Gangitano, & Caramazza, 2001	Grammatical processing	Inferior mid-frontal gyrus	1	5	110% MT	N/A

All these studies used the same paradigm. Studies using off-line TMS with low-frequency stimulation to study cognitive functions are based on the observed decrease in excitability over the primary motor cortex outlasting a block of rTMS (Chen et al., 1997). It is assumed that rTMS-induced reduction in cortical excitability will similarly apply to non-motor cortical areas, allowing us to target different cortical sites to investigate different cognitive domains.

DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; MT= motor threshold; PFC = prefrontal cortex; PPC = posterior parietal cortex; VLPFC = ventrolateral prefrontal cortex.

an area of cortex is exposed (McConnell et al., 2001; Kozel et al., 2000). However, susceptibility to stimulation does not merely reflect the depth of a cortical site. It also depends upon the inherent excitability of the cortex itself, which varies with the specific cortical site being stimulated and the behavioral task being performed.

In the motor cortex, excitability is quantifiable: Stimulation produces a measurable muscle twitch (Rothwell, 1997). Although not capable of producing physical movement, even slight changes of electrical activity in a muscle can be measured using electromyography, the lowest stimulation intensity capable of producing such changes is called the ''motor threshold'' (MT; Rossini et al., 1994). Consequently, stimulation intensities can be normalized across subjects by using multiples of MT. This method takes into account interindividual differences that may modulate the efficacy of magnetic stimulation and provides a composite measure related to the depth of stimulation and cortico-spinal excitability. Using this standardized method may allow comparison across experimental paradigms (Stewart, Walsh, & Rothwell, 2001).

Stimulation over nonmotor areas often does not produce as readily an objective, quantifiable response. Consequently, many studies have used MT as a surrogate marker for excitability across all cortical areas. Yet expecting to gain insight into the excitability of nonmotor areas from stimulating the primary motor cortex may be a fool's errand. The underlying assumption that the effects of TMS across cortical areas are correlated to one another appears to be wrong. For example, accompanying the stimulation of the visual cortex, in some individuals, is the sensation of light called phosphenes (Cowey & Walsh, 2001). In the same manner that an MT can be determined, phosphene thresholds (PTs) can be established in individual subjects (Boroojerdi, Prager, Muellbacher, & Cohen, 2000). PT has been shown to be stable over time within individuals (Stewart et al., 2001). However, there appears to be no intraindividual correlation between PT and MT (Figure 4, Stewart et al., 2001). These differences may be partly explained by differences in skull to cortex distances between motor and visual cortices. Nonetheless, studies have suggested that the scalp to cortex distance at different sites are correlated (McConnell et al., 2001; Kozel et al., 2000). Hence, this factor alone seems unlikely to have broken any potential correlation between the MT and the PT.

Therefore, MT cannot be used to gauge the biological effects of TMS in cortical areas other than the motor cortex. In fact, the situation is even more complex, because even within a single brain area the stimulation intensity that is required to cause cortical disruption varies with the behavioral task. For example, TMS

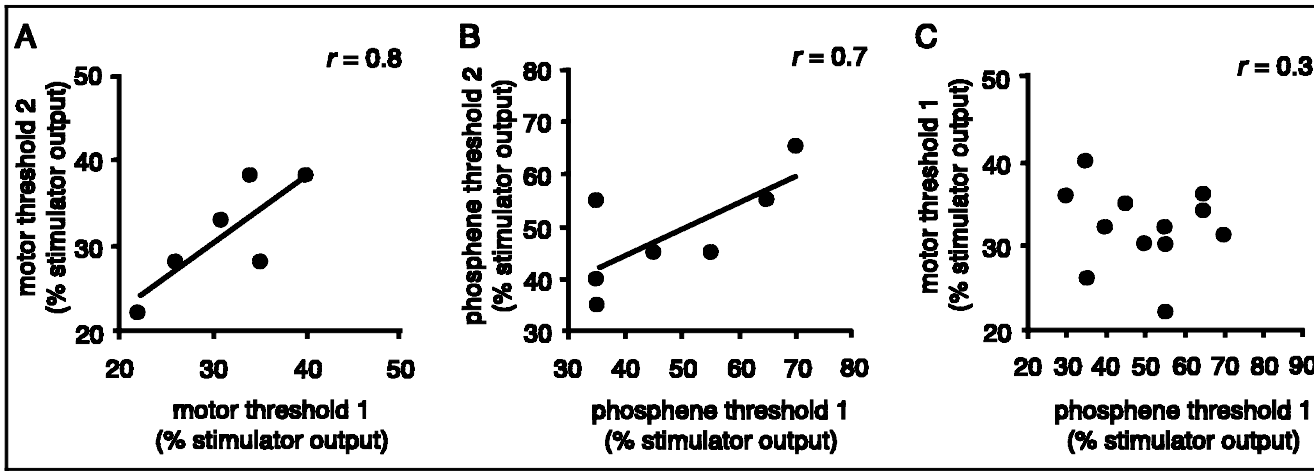

Figure 4. Both a subject's MT (A) and PT (B) correlate between sessions. Despite these consistent measures of cortical excitability, there is no correlation between MT and PT within individual subjects (C, modified from Stewart et al., 2001). This implies that cortical excitability at one site is not a good predictor of excitability at another site. Thus, the rationale of expressing stimulation intensity, outside the motor cortex, as a proportion of MT is doubtful.

of visual cortical area V5 can induce phosphenes (frequently kinetic or moving phosphenes; Pascual-Leone & Walsh, 2001) and can disrupt motion after-effects (MAE, Theoret, Kobayashi, Ganis, Di Capua, & Pascual-Leone, 2002). Repeated determinations of either one of these measures reveal reasonable within-subject reproducibility, but there is no intraindividual correlation of V5-PTs and V5-induced disruption of MAE (Figure 5). Can some better way be found to define stimulation intensity?

Fixed Intensity

Using MT to determine the intensity of TMS over nonmotor areas is arbitrary. Consequently, it might be as well to use a fixed intensity defined by the stimulator output. This approach reduces the experiment duration and limits the number of TMS pulses. Some studies have used such a method (e.g., Lewald, Foltys, & Töpper, 2002; Corthout, Uttl, Walsh, Hallett, & Cowey, 1999; Beckers & Zeki, 1995), which *should* be similar to the MT technique. As in the MT approach, it is likely that for some subjects the fixed intensity will be below that capable of inducing a behavioral effect, giving added variability to the overall results.

Intensity Corrected for Scalp to Brain Target Distance

The strength of the magnetic field produced by a coil falls of exponentially with distance from its center so that the depth of the cortical tissue largely determines magnetic (and induced electric) field strength at a brain site. Consequently, McConnell and collaborators (2001) suggest that the scalp to brain distance should be taken into account when deciding upon stimulation intensity. This method certainly would address *one* important aspect of a brain area's susceptibility to stimulation. However, a major weakness of this approach is that it merely allows a direct calculation of

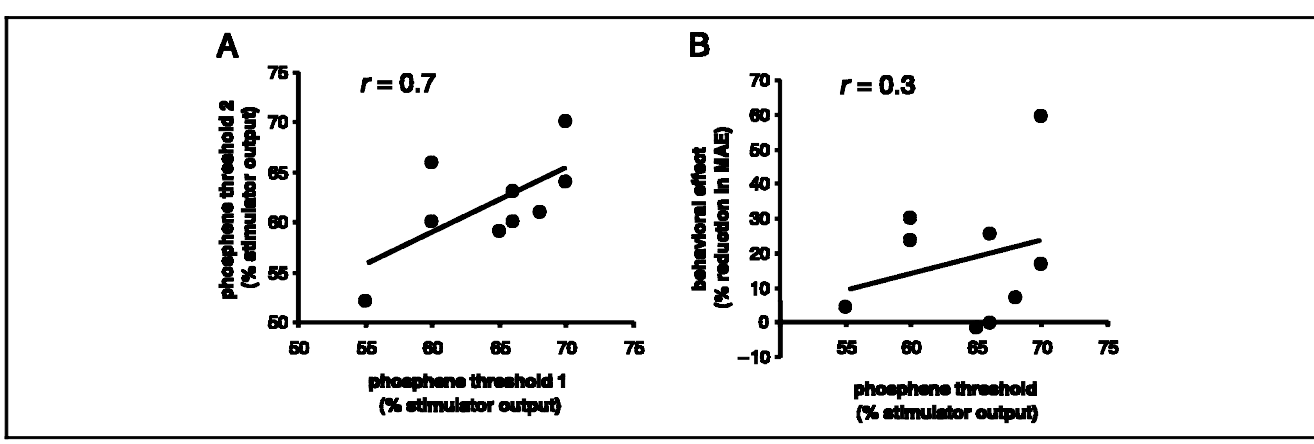

Figure 5. (A) A subject's PT, measured on two separate days, has a good correlation with one another. (B) The PT, however, is poorly correlated with the reduction in MAE that results from applying rTMS over this region. Thus, the magnitude of behavioral change provoked by TMS is not related to cortical excitability as indexed simply by the phosphene threshold (from Théoret et al., 2002). Nor is the behavioral change related to the intensity of stimulation, which is determined by cortical excitability. The MAE was defined as the duration of illusory motion that occurred following adaptation to a 30-sec moving stimulus.

the strength of the magnetic field to which an area of cortex is exposed, but ignores the differential susceptibility of brain areas to a given stimulation intensity depending on individual variations in anatomy and task-related activation.

Intensity Tuning Curve

In the motor cortex, increasing TMS intensity results in increased MEP amplitudes, hence an input–ouput curve can be generated (Chen, 2000). A similar procedure involving a set of increasing intensities while performing a given task would allow a stimulus–response curve design to be applied to the study of cognition. If nonmotor areas behave in a similar fashion to the primary motor cortex, the behavioral effects of TMS should be modulated by different stimulation intensities. Hence, a parametric analysis could be applied, correlating different intensities of stimulation with behavioral consequences.

Behavioral Determination

Some authors have titrated the intensity of TMS for a given experiment by using the robust behavioral effects of stimulation on a different task. In a study of visual cortex excitability, Mulleners, Chronicle, Palmer, Koehler, and Vredeveld (2001) applied TMS at intensities at which ''subjects were unable to identify at least two of the three target letters correctly in the order presented.'' In this manner, stimulation intensities were defined by a behavioral effect of TMS. Similarly, Rushworth, Ellison, and Walsh (2001) used the disruptive effects of rTMS on a visual search task. Behavioral determination of TMS intensities in cognitive studies has the advantage of taking into account the attentional and perceptual capabilities of individual subjects at the time of the experiment. However, the effects of TMS on one task may not necessarily correlate with its effects on another distinct task (e.g., Figure 5).

Functional Determination

The effects of TMS on nonmotor areas can potentially be objectively quantified using imaging techniques. A number of recent studies have elegantly combined functional imaging techniques with TMS to show highly significant changes in cortical blood flow during and following stimulation (Paus et al., 1997; Paus, 2002; Bohning et al., 1999). Blood flow changes within the primary motor cortex are directly related to the intensity of stimulation (Siebner et al., 2001). Consequently, these changes could be used as a surrogate marker of the cortical effects of TMS in areas where it is currently impossible to make such measurements. A similar argument can also be made for the utility of electroencephalography (EEG) monitoring. For example, Paus, Sipila, and Strafella (2001) have shown that single-pulse TMS applied over the motor cortex is associated with a positive (P30) and two negative (N45, N100) scalp potentials. The amplitude of the N45 component is correlated with the intensity of the TMS pulse and appears to be generated in the primary motor cortex. TMS-induced scalp potentials could be used to measure the effects of magnetic stimulation on nonmotor cortical areas. However, the relationship between a cognitive task, its potential disruption and changes in either blood flow, oxygenation, or scalp potentials is uncertain.

Frequency of Stimulation

In single-pulse TMS studies, the interval between pulses has to be sufficiently long to prevent interactions between consecutive pulses. An interval of approximately 7 sec between pulses may be sufficient. No study, however, has systematically investigated this issue. rTMS when applied in an ''on-line'' paradigm (Figure 3) exerts greater disruption of a targeted brain area the higher the stimulation frequency. However, when used in an ''off-line'' design, rTMS frequency appears to determine the neurophysiologic effects. In most instances, while slow-frequency rTMS ($\leq$1 Hz) decreases cortical excitability, high-frequency stimulation ($\geq$5 Hz) increases excitability (Figure 6, Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Berardelli et al., 1998; Pascual-Leone, Grafman, & Hallett, 1994). Following the logic that suppression of cortical activity within a specific cortical target can significantly impair performance (Table 1), an increased excitability could perhaps lead to a behavioral ''improvement.'' Yet we know of no study that has used an ''off-line,'' high-frequency rTMS (i.e., >1 Hz) paradigm to convincingly demonstrate enhanced performance.

In contrast, a few studies applying ''on-line,'' high-frequency rTMS in short trains have actually shown improvements in behavior: Trains applied over Wernicke's

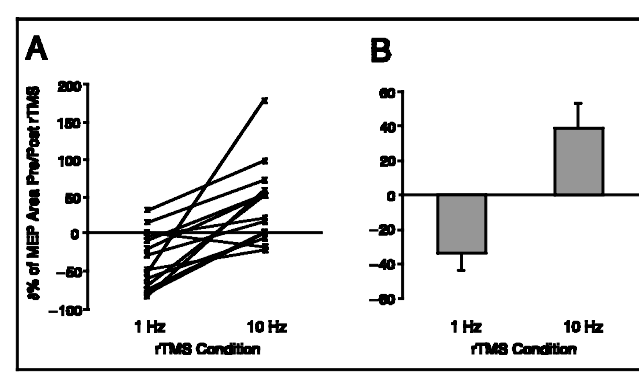

Figure 6. The effect of rTMS on motor cortex excitability (from Maeda et al., 2000). Although as a general rule slow rTMS decreases and rapid rTMS (>1 Hz) increases cortical excitability, there can be great intersubject variability. Some subjects show the opposite pattern (A) but when all participants are averaged (B) the general rule holds true.

area gave a response time advantage for processing black-and-white drawings (naming: Mottaghy et al., 1999; and reasoning: Boroojerdi et al., 2001). Similar performance improvements have been elicited by single-pulse stimulation in both the healthy (Grosbras & Paus, 2002; Töpper, Mottaghy, Brugmann, Noth, & Huber, 1998) and diseased brain (Oliveri et al., 1999). The precise neurologic mechanisms underlying such behavioral improvements remain at best uncertain. Potentially, TMS may induce a paradoxical functional facilitation, where behavioral improvement is due to the disruption of a brain region that normally exerts inhibitory influences on distant brain areas (Kapur, 1996). Similar behavioral gains have been found in studies applying ''off-line'' 1-Hz rTMS, presumably inhibiting the targeted brain region and releasing distant brain areas (Hilgetag, Theoret, & Pascual-Leone, 2001)

Duration of Stimulation

Lengthening the duration of ''on-line'' rTMS is presumed to cause more disruption, by virtue of temporal summation of the effects of the stimulation. However, longer trains at high stimulation frequencies are increasingly risky as a seizure can be induced (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994). Therefore, the duration of the ''on-line'' rTMS trains is primarily limited by current safety guidelines aimed at minimizing the risk of side effects (Wassermann, 1998). These and the relevant national guidelines should be considered mandatory reading for anyone contemplating using TMS (Hallett, Wassermann, Pascual-Leone, & Valls-Sole, 1999; Wassermann, 1998; Pascual-Leone et al., 1993). It is unclear whether for safety or scientific reasons there should be a limit to the duration of single-pulse TMS studies. No study has addressed the question of the number of single TMS pulses that can be applied in a given session.

The duration of ''off-line'' rTMS in cognitive studies has been based on data obtained from the motor cortex. These seem to indicate that longer trains induce longer-lasting and more robust effects. For example, stimulating the primary motor cortex for 4 min at 1 Hz did not significantly reduce cortical excitability, but increasing train duration caused a reduction in cortical excitability (Maeda et al., 2000). However, no systematic, parametric study is available and consequently, determination of train duration has been mostly arbitrary across studies (Table 1). The confusion is further increased by the uncertainty about whether these observations can be appropriately extrapolated to nonmotor areas.

Duration of the Stimulation Effect

Little is known about the duration of the effects, neurophysiologic or behavioral, of single TMS pulses or rTMS trains. It is presumed that single TMS pulses exert a very limited effect of around 100–500 msec. After approximately 200 msec, for example, the function of the parietal lobe returns to normal allowing reaching movements to compensate for changes in target position (Desmurget et al., 1999). The behavioral effects of ''on-line'' rTMS are generally assumed to be limited to the duration of the rTMS train itself. This is, however, unlikely given the experience with ''off-line'' rTMS. Presumably, the behavioral effects during ''on-line'' rTMS appear more dramatic, but subtle neurophysiologic and behavioral consequences of stimulation probably outlast the rTMS train. These lasting rTMS effects constitute the basis for the ''off-line'' rTMS paradigms. Neurophysiologic studies (e.g., EEG studies during single-pulse or ''on-line'' rTMS) should be able to provide more detailed insights into this important issue.

In the motor cortex, a 15-min train of rTMS at approximately 1 Hz reduces cortical excitability for at least the subsequent 15 min (Chen et al., 1997). Two studies have specifically addressed the question of how long the behavioral effects can outlast the application of rTMS. In one study, a 1-Hz rTMS 600 pulse train over the parietal cortex induced a shift in the lateralization of interaural time differences for at least 11 min (Table 1, Lewald et al., 2002). A similar approach, also using a 10-min 1-Hz train, demonstrated visual working memory impairments following rTMS over prefrontal areas which lasted only 5 min (Figure 7, Table 1, Mottaghy, Gangitano, Sparing, Krause, & Pascual-Leone, 2002). Further behavioral and neurophysiologic studies are critically needed to gain further insights that can aid in the design of optimized experimental paradigms.

Stimulation Parameters and Behavioral Task

The behavioral deficits induced by TMS do not simply depend upon the selected stimulation parameters. Instead, they are the products of an interaction between the disruption caused by TMS to the targeted brain site, the effects to distant brain areas along functional connections, and the particular task being performed. Hence, a cognitive task may be sufficiently trivial that despite substantive disruption to normal cortical function there may be no observed behavioral impairment. Similarly, a stimulation paradigm may produce a relatively subtle disruption to cortical function so that only a complex cognitive task would reveal any impairment. With the inherent redundancy of the brain and its resulting high capacity to compensate for disruption caused by TMS, it is perhaps only through straining the available neuronal resources with a reasonably complex task that it becomes possible to observe behavioral impairment. This relationship between task complexity, cortical disruption, and impairment was demonstrated in a recent study exploring the effects of rTMS of the parietal cortex (1 Hz, 10 min) on visual spatial attention (Hilgetag et al., 2001). To control for interindividual differences in acuity and attention, the visual stimuli were adapted for each participant. This

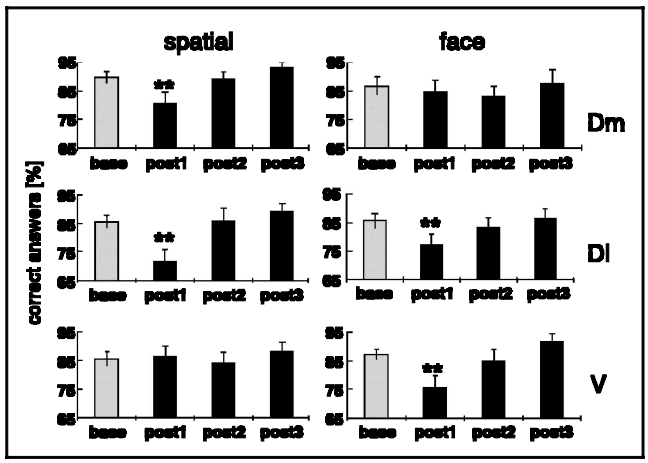

Figure 7. Shows the effect upon working memory performance of "off-line" rTMS at different sites over the prefrontal cortex (Dm = dorsomedial prefrontal cortex; Dl = dorsolateral prefrontal cortex; V = ventrolateral prefrontal cortex). Two distinct working memory tasks were used: one involved recalling the position of a stimulus (spatial) while the other required recollection of a person's face (face). The mean performance rates in percent with error bars (standard error of the mean) are shown for each stimulation site and each working memory task (spatial and faces) at the four different time points (base = baseline; post1 = immediately after rTMS; post2 = 5 min after rTMS; post3 = 10 min after rTMS). Significant decreases in performance ($p < .05$) following rTMS are marked (**). The more dorsal sites of stimulation cause impairment in spatial working memory. In contrast, it is the ventral sites which are responsible for nonspatial (e.g., facial) working memory, suggesting a relative segregation of spatial and nonspatial working memory across the prefrontal cortex (Mottaghy et al., 2002).

approach maximized the potential disruptive and facilitative effects of rTMS on task performance.

WHERE ARE YOU STIMULATING?

One of the most substantial problems in the study of cognition with TMS is relating the known stimulation site in the overlying scalp with a particular brain area, in other words, the problem of anatomical localization. The relationship between scalp position and a given brain area is variable across individuals, hence the placement of a TMS coil on the scalp according to bony landmarks will necessarily introduce errors and interindividual variability in the targeted brain region (Meyer, Britton, Kloten, Steinmetz, & Benecke, 1991). A potential solution to this problem is to define coil position based upon objective output parameters. This is relatively easy to achieve over the primary motor cortex, where magnetic stimulation can result in an overt response (muscle twitch). Similarly, the induction of phosphenes over the visual cortex can also be used to guide coil location (Cowey & Walsh, 2001). However, in cortical areas where no overt responses to TMS can be elicited, appropriate placement of the coil can be a substantially more complicated task.

A possible approach is to locate brain areas relative to those that have a reasonably certain position. For example, the dorsolateral prefrontal cortex can be defined as 5 cm anterior to the thumb representation over the primary motor cortex as measured using the Talairach atlas (Pascual-Leone, Rubio, Pallardo, & Catala, 1996; Pascual-Leone, Wassermann, et al., 1996). However, when attempting to validate this procedure by comparing the Talairach position against the known brain anatomy from individual brain scans, the final location of the coil relative to the underlying Brodmann's area was found to be quite variable (Herwig, Padberg, Unger, Spitzer, & Schönfeldt-Lecuona, 2001; Pascual-Leone, Bartres-Faz, & Keenan, 1999).

Another approach is to use a frameless stereotactic system to provide "on-line" information about the location of the coil (Gugino et al., 2001; Herwig et al., 2001; Paus, 1999). A structural brain MRI is obtained prior to the TMS session and is displayed on a computer monitor. Sensors are attached to the stimulating coil and to the subject's head; both monitored by a position sensor. This information is sent to a computer, which after a calibration procedure displays the position and orientation of the coil on the MRI. Image-guided TMS permits constant visualization of coil placement in relation to the subject's brain. However, the assumption that the gross anatomical features of the cerebral cortex (e.g., mid-frontal gyrus) are related to its functional subdivisions (e.g., Brodmann's areas, i.e., BA 46) is certainly questionable. Fortunately, frameless stereotaxy can also be used in conjunction with functional neuroimaging, allowing activated sites to be targeted for stimulation. This reduces the influence of interindividual anatomical variability and no longer assumes a correspondence between anatomical landmarks of the cerebral cortex and task-related functional activations.

Although these approaches offer enhanced anatomical precision, this does not necessarily translate into providing TMS studies of cognition with substantially improved accuracy. Even relatively conservative estimates suggest that single-pulse TMS effects cortical tissue over 1 cm from the center of the coil (Wilson, Thickbroom, & Mastaglia, 1993; Brasil-Neto et al., 1992). Inevitably, with rTMS this affected zone is likely to be larger; consequently, the high precision offered by navigational systems is swamped by a more substantial source of error, which is inherent within the technique. At this point we should view TMS as providing a method to dissociate and explore aspects of human behavior and cognition without necessarily giving a particularly detailed account of the precise anatomical zone effected by TMS. For example, it has been possible to dissociate working memory systems across the prefrontal cortex, with the dorsolateral area providing a critical contribution to spatial while nonspatial working memory was supported by the ventrolateral area (Figure 7, Mottaghy et al., 2002). Improved, more focal TMS coils are needed to gain sufficient

spatial resolution to derive all the possible benefits of using a combination of frameless stereotaxy and TMS. Such coils are going to be essential when TMS is being used to alter cortical excitability, as is generally the case in cognitive studies.

TMS can also be used to measure cortical excitability. When applied in this context, remarkable spatial resolution can be achieved with current devices. For example, while learning a sequence of finger movements, a TMS study has shown that the representation of the hand over the primary motor cortex expands considerably until subjects become aware of the underlying pattern (Pascual-Leone, Grafman, et al., 1994). When awareness is achieved, the hand representation suddenly contracts down to baseline levels. Similar changes have been observed in piano players and athletes (Pearce, Thickbroom, Byrnes, & Mastaglia, 2000; Pascual-Leone et al., 1995). Being able to resolve these changes is a testament to the spatial accuracy of TMS when used to measure rather than alter cortical excitability. These studies have been extended to include measurement of changes in intracortical excitability during the acquisition of skills (Nordstrom & Butler, 2002) providing insights into the neural mechanisms supporting procedural learning.

WHAT ARE YOU STIMULATING?

Each area of the brain is coupled through anatomical connections and projections with a vast number of other areas. Hence, stimulating an area of the brain may have functional consequences not only at that site but throughout a neuronal circuit. Potentially, this makes the interpretation of any behavioral impairment fraught with difficulty for it may represent the ability of the rest of the brain to compensate for disruption either within an area or across a circuit. In accord with this view are functional imaging studies demonstrating substantial activity changes even in brain areas distant from the actual site of stimulation (Bohning et al., 1999; Paus et al., 1997). Even these studies may underestimate the circuit affected by magnetic stimulation. Projections arising from an area being stimulated are likely to be activated orthodromically leading to an increase in metabolic demands in a distal site reflected in a rise in blood flow (Paus et al., 1997; Wong & Moss, 1992). In addition, anatomical projections to this site are also likely to be activated antidromically. Although this activation may influence distal sites, it will be without a direct change in synaptic activity. Consequently, there may be neither changes in metabolic demands nor blood flow. Perhaps the differential effects upon blood flow produced by orthodromic and antidromic stimulation may explain why a larger network of areas is not visualized (Wong & Moss, 1992). For example, stimulation of the frontal eye field (Paus et al., 1997) did not result in a significant increase in blood flow to the dorsolateral prefrontal cortex, as may have been anticipated (Buttner & Fuhry, 1995; Funahashi, Bruce, & Goldman-Rakic, 1991). Alternatively, these blood flow patterns may provide a description of the functional connectivity as opposed to an accurate anatomical description of the human brain. Regardless, an entire circuit not just a single brain area is effected by stimulation, making the interpretation of behavioral effects difficult.

Cortical areas distant from the primary site of stimulation have shown not only blood flow changes but also alterations in excitability (Munchau, Bloem, Irlbacher, Trimble, & Rothwell, 2002; Gerschlager, Siebner, & Rothwell, 2001). The primary motor cortex has a reduced excitability following 20 min of 1-Hz stimulation at 80% of MT over the premotor cortex. These two areas are richly interconnected, consequently, it is not too surprising that altered activity within the premotor cortex produces detectable changes within the primary motor cortex. Nonetheless, these observations serve to demonstrate that rTMS does not merely affect the neuronal activity of a single site but rather a network. Such distant effects may also influence subcortical structures. These problems are substantially reduced when using single pulses of TMS to disrupt cognition (Pascual-Leone, Walsh, & Rothwell, 2000).

Although these studies demonstrate the activation and potential disruption of an entire circuit, this is very far indeed from showing that distant effects are responsible for the observed behavioral effects of TMS. It is quite possible that the principal component responsible for behavioral changes remains the primary area being stimulated, with other more distant sites having at best only a marginal influence upon a particular behavior. For example, studies examining the contribution of the prefrontal cortex to working memory have shown quite a surprising degree of specificity (Mottaghy et al., 2002). Stimulation over the dorsolateral region of the prefrontal cortex produces specific deficits in spatial working memory, leaving verbal working memory relatively preserved. Stimulation over the ventrolateral prefrontal cortex results in the opposite behavioral results. These effects are spatially specific despite the interconnections among areas of the prefrontal cortex. However, in some circumstances, the distant effects of TMS may best explain the observed behavioral effects. These explanations could include the release of neurotransmitters from a distant site (Strafella, Paus, Barrett, & Dagher, 2001) or its functional release from tonic inhibition following the direct stimulation of a brain area (Hilgetag et al., 2001; Oliveri et al., 1999). Interpreting the effects of TMS upon behavior is a substantial problem. We always run the considerable risk of offering a post hoc explanation for any pattern of behavior resulting from TMS by invoking a combination of both primary and distant site effects. We may only be freed from this problem by using a hypothesis-driven approach. What is true generally in science, is also true of TMS studies: Paradigms should be set up

specifically to refute a particular concept or in an attempt to dissociate between possible contributions to behavior. Although such a hypothesis-driven approach is laudable, with such an immature discipline as cognitive neuroscience there still needs to be room for a more data-driven approach with some experiments being truly exploratory in nature. In such studies, the simplest explanation should perhaps be given the greatest credence whether this involves known aspects of the primary or distant sites.

CONCLUSIONS

We have described and, where possible, explained some of the perils and pitfalls of applying TMS in cognitive studies. It may appear to the unwary reader that we have been cheated: In exchange for a single problem, we now have many distinct problems each requiring a solution. However, the single problem was one of determining the contribution made by a cortical area to an aspect of behavior, by no means trivial and one which has plagued much of contemporary cognitive neuroscience. This has been replaced, admittedly with many more problems, but these are simpler. Given time, many of these will be solved or shown not to be as problematic as we had once feared. Some have already been solved or can at least be ameliorated by using carefully designed experiments. Nonetheless, these difficulties should not have us turn away in despair. Rather, we need to increasingly understand and meet the challenges set by integrating TMS into cognitive studies. The alternative is to risk loosing a potentially unique opportunity to deepen our understanding of human cognition.

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