

Transcranial Magnetic Stimulation

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I. Introduction

The term "brain mapping" is not restricted to techniques that can produce a visual or anatomical map of the brain. Several techniques provide other kinds of maps with coordinate systems based in temporal events rather than spatial measurements (ERPs and MEG for example) or behavior (experimental psychology). The task for integrated brain mapping is to find methods, or a language, for making the translations between these different kinds of maps meaningful. The methods available to the neuroscientist can be conceived as occupying different problem spaces according to whether the strength of the technique is based on temporal or spatial resolution (Fig. 1). In this chapter we outline some of the important features and uses of transcranial magnetic

stimulation (TMS), a technique that occupies a unique problem space because of the combination of its spatial and temporal resolution and the fact that it is used to stimulate the brain rather than record electrical or metabolic activity.

TMS is a neurophysiologic technique that allows the induction of a current in the brain using a magnetic field to cross the scalp and the skull safely and painlessly. The first example of a physiological effect due to a time-varying magnetic field was reported by d'Arsonval in 1896, who produced phosphenes when a volunteer's head was placed inside a coil driven at 42 Hz. However, it was Anthony Barker and colleagues who in 1984 succeeded in developing a magnetic stimulator that delivered field pulses short enough to allow recording of evoked nerve and muscle action potentials. Since then, there has been a marked increase in the number of magnetic stimulators used clinically and in research worldwide (Pascual-Leone and Meador, 1998). TMS can be used to complement other neuroscience methods in the study of central motor pathways, the evaluation of corticocortical excitability, and the mapping of cortical brain functions. In addition, TMS provides a unique methodology to determine the true functional significance of the results of neuroimaging studies and the causal relationship between focal brain activity and behavior. The origins and development of TMS lie in medical

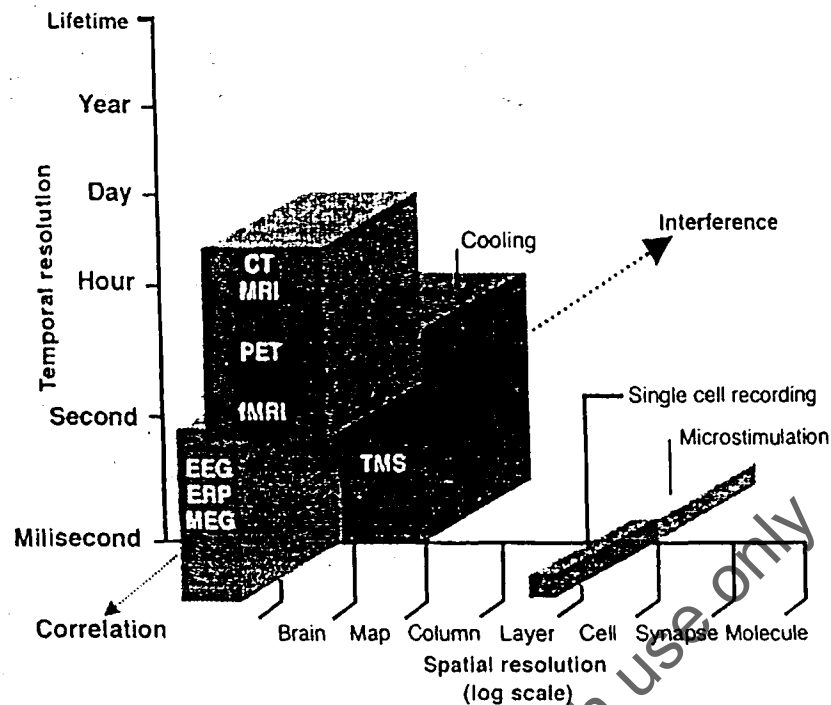


Figure 1 The place of TMS in neuropsychological studies is best thought of in terms of the "problem space" it occupies. The spatial and temporal resolution of TMS compared with other techniques is shown. However, it is not just space and time that make TMS indispensable: it is the ability of TMS transiently to interfere with functions whereas other techniques correlate brain activity with functions. The different volumes occupied by each of the techniques reflect that fact that when one selects a technique, one is also making a selection about the kind of question one can ask within the defined problem space. Reproduced from Walsh and Cowey (2000), with permission.

physics and clinical neurology and these fields have been reviewed in depth by Barker (1999), Mills (1999), George and Belmaker (2000), and Pascual-Leone *et al.* (2002). In the past 5 years in particular there has been rapid development of the use of TMS in cognitive neuroscience, to study psychological questions of vision, attention, memory, or language, and some of these have been studied in the context of plasticity and development. The cognitive neuroscience advances have been reviewed comprehensively elsewhere (Walsh and Cowey, 1998, 2000; Pascual-Leone *et al.*, 1999a, 2000; Walsh and Rushworth, 1999; Rushworth and Walsh, 1999). Our aim in this chapter is to give a brief introduction and overview to the range of different uses to which TMS can be put and in particular to highlight the areas where TMS interfaces with other techniques available (see also Paus' chapter).

II. Basic Principles of Magnetic Brain Stimulation

The basis of magnetic stimulation is electromagnetic induction, which was discovered by Faraday in 1831. A pulse of current flowing through a coil of wire generates a magnetic field. The rate of change of this magnetic field determines the

induction of a secondary current in any nearby conductor. In TMS, a current passes through a coil of copper wire that is encased in plastic and held over the subject's head. As a brief pulse of current is passed through the stimulating coil, a magnetic field is generated that passes through the subject's scalp and skull without attenuation (only decaying by the square of the distance). This time-varying magnetic field induces a current in the subject's brain. Therefore, TMS might be best considered a form of "electrodeless, noninvasive electric stimulation."

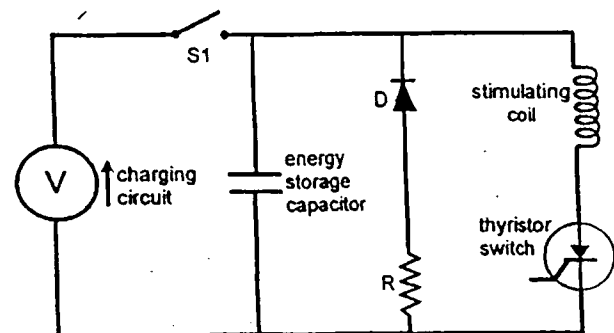


Figure 2 Schematic diagram of a standard (single-pulse) magnetic nerve stimulator. Reproduced from Barker (1999), with permission.

In 1985 Barker *et al.* successfully applied a magnetic pulse over the vertex of the human scalp and elicited hand movements and measured electromyographic (EMG) activity from the first dorsal interosseus (Barker *et al.*, 1985). The basic circuitry of the magnetic stimulator is shown in

Fig. 2. A capacitor charged to a high voltage is discharged into the stimulating coil via an electrical switch called a thyristor. This circuitry can be modified to produce rapid, repetitive pulses that are used in repetitive TMS (rTMS). Figure 3 shows the whole sequence of events in TMS from

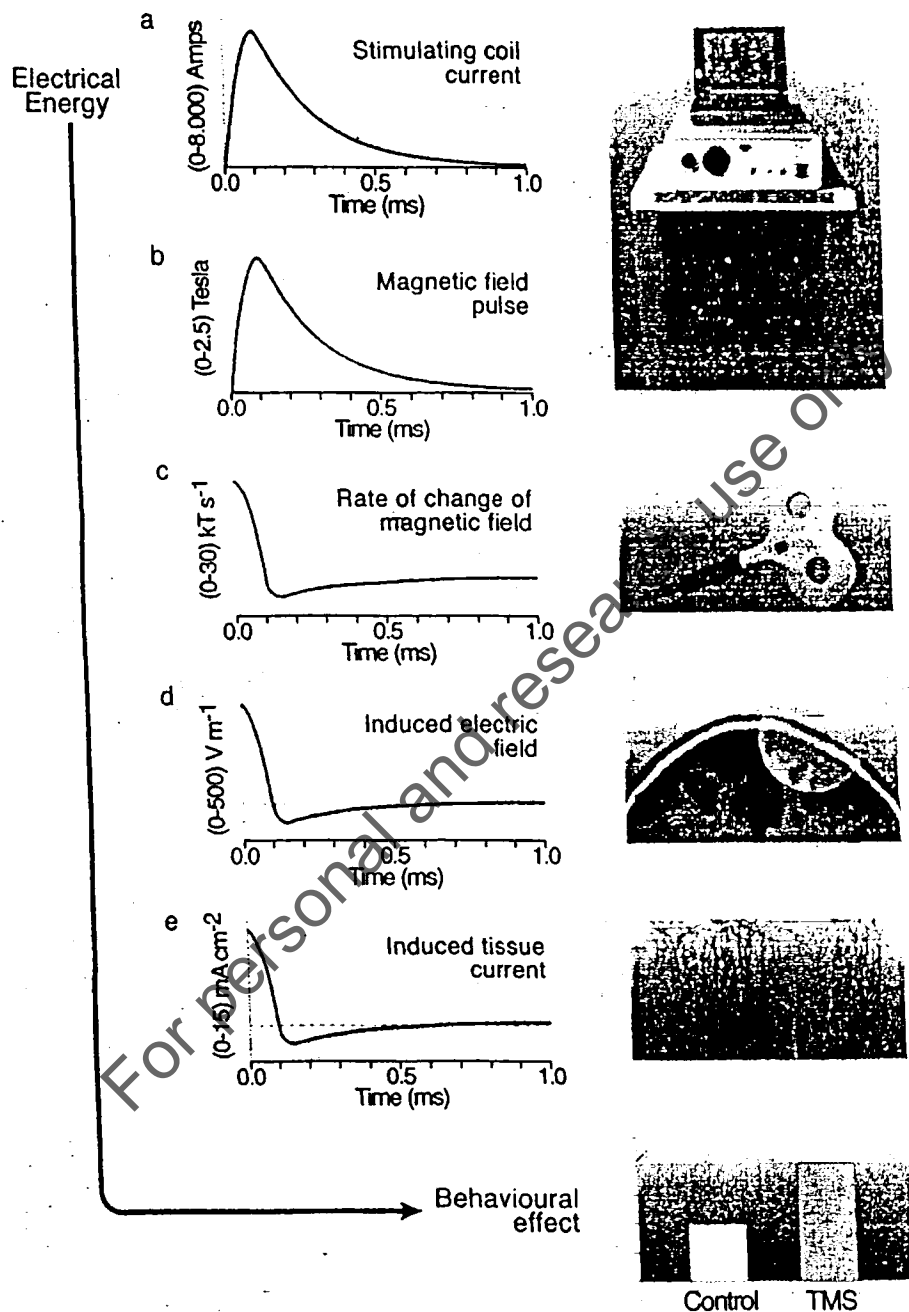


Figure 3 The sequence of events in TMS. An electrical current of up to 8 kA is generated by a capacitor and discharged into a circular, or figure-8-shaped, coil which in turn produces a magnetic pulse of up to 2 T. The pulse has a rise time of approximately 200 μ s and a duration of 1 ms and, due to its intensity and brevity, changes at a rapid rate. The changing magnetic field generates an electric field resulting in neural activity or changes in resting potentials. The net change in charge density in the cortex is zero. The pulse shown here is a monophasic pulse but in studies that require rTMS the waveform will be a train of sine-wave pulses, which allow repeated stimulation. Reproduced from Walsh and Cowey (2000), with permission.

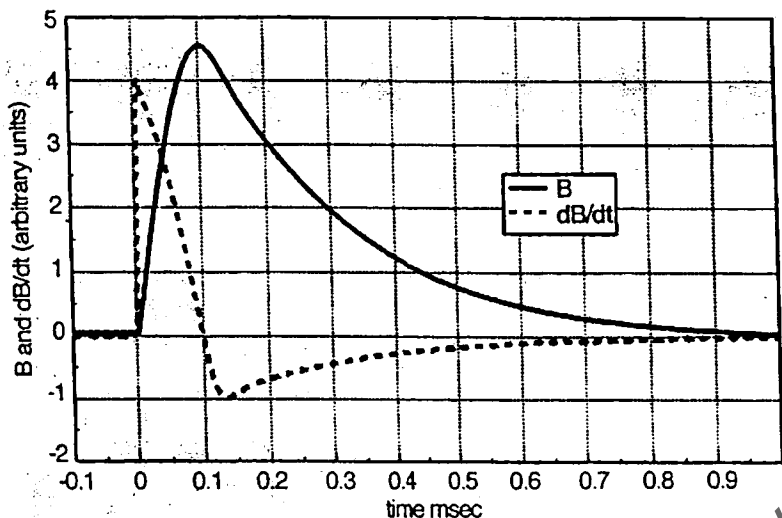


Figure 4 The time course of the magnetic field (B) produced by a single-pulse stimulator at the center of a stimulating coil and the resulting electrical field (dB/dt) waveform (Magstim 200 stimulator). Reproduced from Barker (1999), with permission.

the pulse generation to cortical 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 these requirements the current is delivered to the coil with a very short rise time (approx 200 μ s) and the pulse has an overall duration of approximately 1 ms. These demands also require large energy storage capacitors and efficient energy transfer

from capacitors to coil, typically in the range of 2000 joules of stored energy and 500 joules transferred to the coil in less than 100 μ s. The induced field has two sources (Roth *et al.*, 1991). One is the induction effect from the current in the coil (and this is what is usually meant when discussing TMS); the other is a negligible accumulation of charge on the scalp or between the scalp and the skull. Figures 4 and 5 show the difference between two types of pulses, monophasic and biphasic, that can be produced by magnetic stimulators. The biphasic waveform generally used in rTMS machines differs

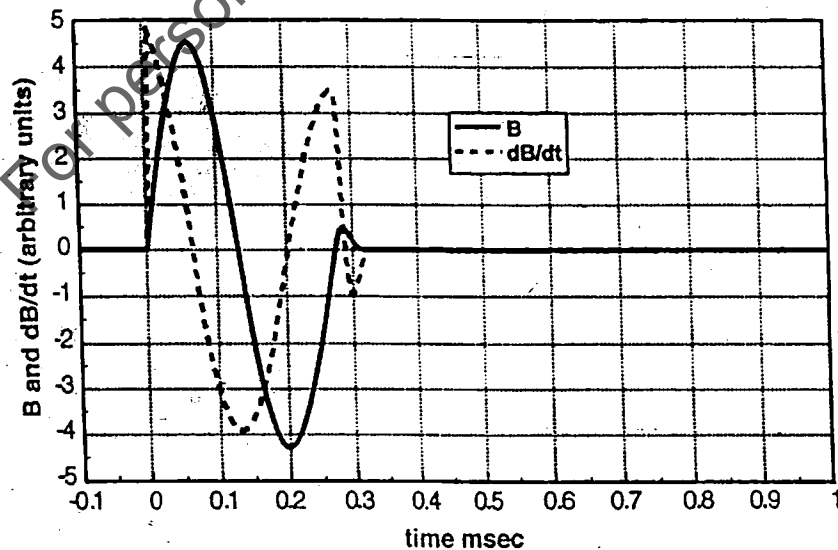


Figure 5 The time course of the magnetic field (B) produced by a biphasic repetitive-pulse stimulator at the center of a stimulating coil and the resulting electrical field (dB/dt) waveform (Magstim Rapid stimulator). Reproduced from Barker (1999), with permission.

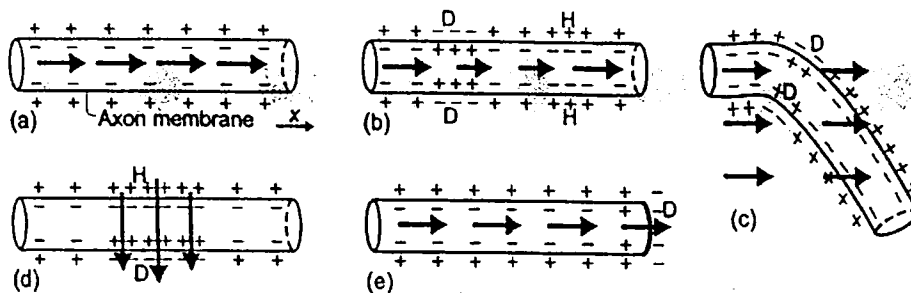


Figure 6 How current flow may activate neurons: schematic illustrations of activation mechanisms. In (a) the current flow in a uniform electric field runs parallel to a neuron and thus causes no change in transmembrane current. In (b) there is a gradient activation due to a nonuniform field along the axon which causes change in transmembrane potentials resulting in action potentials. In (c) the same relationship and end result is seen as in (b), but here the change in transmembrane current is due to spatial variation (bending) of the nerve fiber rather than inhomogeneities in the electric field. In (d) the depolarization is caused by transverse activation of neuron by the induced electric field and (e) represents changes in activation at the axon terminal. Regional depolarization and hyperpolarization are indicated by D and H, respectively. Reproduced from Ruohonen and Ilmoniemi (1999), with permission.

from the monophasic in two ways. First, in the biphasic mode up to 60% of the original energy in the pulse is returned to the capacitor, rendering rTMS more energy efficient and thus enabling the capacitors to recharge more quickly (Jalinous, 1991; Barker, 1999). More importantly for the end user, the biphasic waveform seems to require lower field intensities to induce a current in neural tissue (McRobbie and Foster, 1984). The reasons for the higher sensitivity of neurons to biphasic stimulation have been examined with respect to the properties of the nerve membrane (Reilly, 1992; Wada *et al.*, 1996). The rise time of the magnetic field is important because neurons are not perfect capacitors, they are leaky, and the quicker the rise to peak intensity of the magnetic field, the less time is available for the tissue to lose charge. A fast rise time has other advantages in that it decreases the energy requirements of the stimulator and the heating of the coil (Barker, 1999).

In magnetic stimulation an electric field is induced both inside and outside the axon (Nagarajan *et al.*, 1993). To produce neural activity the induced field must differ across the cell membrane. As Fig. 6 shows, if the field is uniform with respect to the cell membrane, no current will be induced; either the axon must be bent across the electric field or the field must traverse an unbent axon. Another way of stating what is visualized in Fig. 6 is that the probability of an induced field activating a neuron is a function of the spatial derivative of the field along the nerve membrane—in Barker's words "the activating function is proportional to the rate of change of the electric field" (Barker, 1999; Reilly, 1992; Abdeen and Stuchley, 1994; Garnham *et al.*, 1995; Maccabee *et al.*, 1993).

The principle of the activating function can be used as a guide in thinking about the site of stimulation. Amassian *et al.* (1992) have modeled the stimulation of bent neurons

and calculated that the excitation of straight nerves occurs near the peak electric field, whereas the activation of bent nerves occurs at the positive peak of the spatial derivative. Presumably, where the field and neuron lie in almost the same plane, the spatial derivative is equivalent to the peak field. The different orientations of neurons in the cortex preclude a simple one-to-one mapping from electrical fields in homogeneous conductors to the volume of neural tissue affected. Amassian gives a practical example of how knowledge of the anatomy of the cortical area being stimulated underlies accurate interpretation of the effects of TMS (Fig. 7).

A. Stimulating Coils

Stimulating coils consist of one or more well-insulated coils of copper wire frequently housed in a molded plastic cover. Stimulating coils are available in a variety of shapes and sizes. The two types of coil in most common use are circular and figure of 8 in shape and the regions of effective stimulation produced by these two configurations depend on the geometry of the coil and of the neurons underlying the coil and on local conduction variability. In addition to differences in focality of the induced current, circular and figure-8 coils may differ in the neural structures activated within the brain. Therefore, the stimulating coil employed should be carefully chosen and always considered when interpreting results of TMS studies.

Figure 8 shows the distribution of an induced electric field under a round coil (top) and Fig. 9 (top) the distribution of the spatial derivative of the field with respect to a straight axon that will be hyperpolarized at B and polarized at A ("virtual anode" and "virtual cathode," respectively, in Barker's terminology). Nerves lying tangential to any other

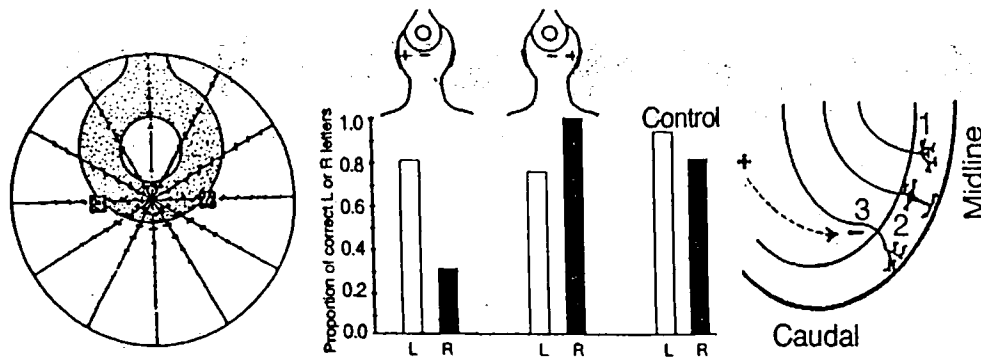


Figure 7 The electric field induced by TMS delivered by a round coil is here modeled (left) in a spherical saline volume conductor. The effect on visual detection of reversing the polarity of the induced electric field is shown (middle) and a schematic of the possible sites of stimulation are shown (right). The clockwise current in the coil (left) induces an anticlockwise electric field and the field intensity diminishes with distance from the peak of stimulation (center of spherical saline bath). The results from one subject show that reversing the direction of the induced field differentially suppresses visual performance in the left or right visual hemifield (Amassian *et al.*, 1994). The most likely point of stimulation is the bend in the axon (3). Excitation of the axonal arborizations (1) is less likely due to relative high resistance, and excitation of the dendritic arbors (2) is less likely due to relative reduced electrical excitability. Reproduced from Amassian *et al.* (1998), with permission.

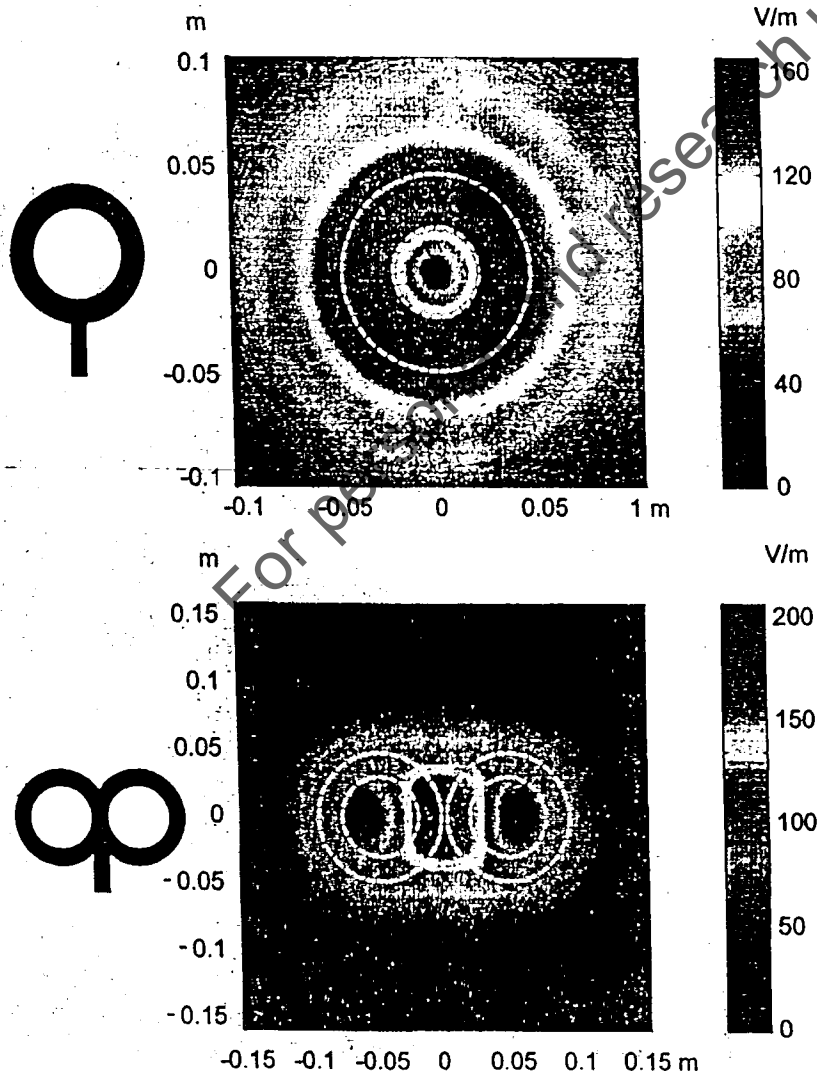


Figure 8 Distribution of the induced electric fields by a circular (top) and figure-8 (bottom) stimulating coil. The circular coil has 41.5-mm inside turn diameter, 91.5-mm outside turn diameter (mean 66.5 mm), and 15 turns of copper wire. The figure-8 coil has 56-mm inside turn diameter, 90-mm outside turn (mean 73 mm), and 9 turns of copper wire on each wing. The outline of each coil is depicted with dashed white lines on the representation of the induced fields. The electric field amplitude is calculated in a plane 20 mm below a realistic model of the coil ($dI/dt = 10^6 \text{ A s}^{-1}$). Figure created by Anthony Barker.

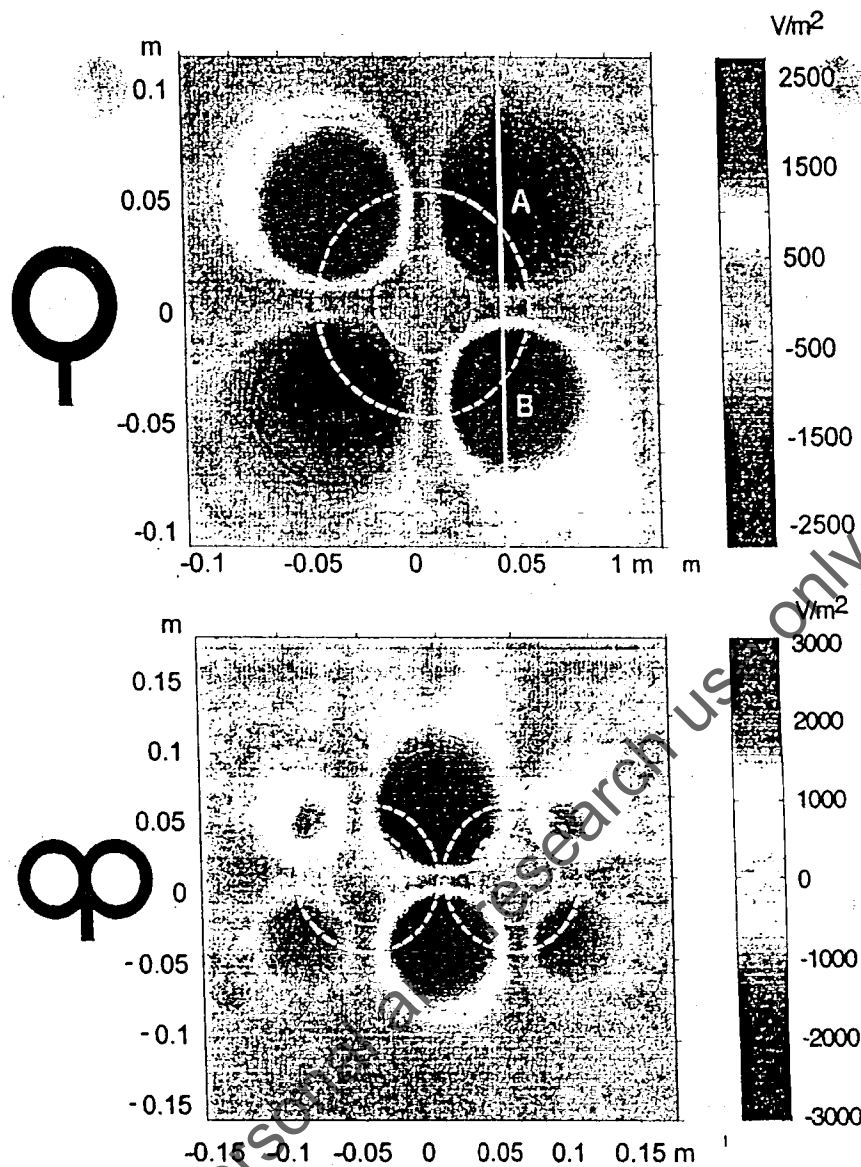


Figure 9 Rate of change of the electric field calculated in the direction of the nerve along the axis AB, measured in the same plane as with coils shown in Fig. 8. Figure created by Anthony Barker.

part of the coil will be similarly stimulated. This does not mean that the effects of TMS are restricted to the cortical area located precisely under the windings of the coil. The neurons receiving stimulation will activate their neighbors and also affect the organization of other interacting pairs of neurons. With this round coil, making contact between only one arc of the coil and the scalp can increase specificity of the area stimulated. The side of the coil with which stimulation is applied will also affect the outcome. With a monophasic pulse, the current travels clockwise with respect to one face of the coil and counterclockwise with respect to the other. This can be used to bias stimulation in one or the other direction and has been used to selectively

stimulate one or the other hemisphere while apparently stimulating in the midline (Amassian *et al.*, 1994; Meyer *et al.*, 1991) and to enhance the efficacy of motor cortex stimulation by applying the current direction optimal for stimulation of that region (Brasil-Neto *et al.*, 1992a,b).

Stimulation with a figure-8 coil increases the focality of stimulation (Ueno *et al.*, 1988). This configuration is of two circular coils that carry current in opposite directions and, where the coils meet, there is a summation of the electric field. Figures 8 (bottom) and 9 (bottom) show the induced electric field and the rate of change of the field with respect to a straight neuron. In addition to the new "summed" anode and cathode produced by the figure-8 coil, the two

separate windings maintain their ability to induce a field under the outer parts of the windings. However, in experiments in which the center of the figure of 8 is placed over the region of interest, the outer parts of the coil are usually several centimeters away from the scalp and thus unlikely to induce effective fields.

B. Single-Pulse, Paired-Pulse, and Repetitive TMS

TMS can be applied as single pulses, delivering one stimulus every 3 or more seconds to a given cortical region; as pairs of stimuli separated by a variable interstimulus interval of a few milliseconds; or as trains of stimuli at variable frequency delivered to the same brain area for several seconds (Fig. 10).

Paired-pulse TMS can be applied with the two stimuli of the same or different intensities delivered through a single coil to the same brain region. In this manner, paired-pulse TMS can be used to study corticocortical inhibitory and excitatory circuits. Alternatively, paired-pulse TMS can be applied using two coils so that each of the two stimuli affects a different brain region. Using this methodology, paired-pulse TMS can be used to study corticocortical connectivity and interactions.

Repetitive TMS can be applied at relatively slow frequency, delivering one stimulus every second or less. This form of stimulation is referred to as slow (or low frequency) rTMS. Alternatively, rTMS can be applied at higher stimulation frequencies, with stimuli delivered up to 20 times per second. We then speak of rapid or high-frequency rTMS. Slow and rapid rTMS appear to exert differential modula-

tory effects on cortical excitability (Pascual-Leone *et al.*, 1994a). Furthermore, the differentiation of slow and rapid rTMS is meaningful from the point of view of safety of the technique (Wassermann, 1998).

A single TMS pulse can depolarize a population of neurons and hence evoke a given phenomenon or percept. When applied to the motor cortex, a single TMS pulse of sufficient intensity can induce a movement in a contralateral limb, and when applied to the visual cortex it can induce the perception of a flash of light (phosphenes). In addition, a single TMS pulse can transiently disrupt normal brain activity by introducing random neural activity into the stimulated area (see Walsh and Cowey, 2000). If the targeted brain area is *necessary* for the completion of a given task, performance should be impaired. Single TMS pulses disrupt activity for only some tens of milliseconds and provide information on *when* activity contributes essentially to task performance (the "chronometry" of cognition). In this fashion, applied to the motor cortex, single-pulse TMS can investigate the timing of the engagement of the motor cortex in the execution of motor programs (Day *et al.*, 1989a); applied to the somatosensory cortex it can provide insight into the time course of tactile perception (Cohen *et al.*, 1991a); and applied to the occipital cortex it can explore the chronometry of detection and perception of visual stimuli (Amassian *et al.*, 1989).

rTMS offers the advantage of an "offline" paradigm in which magnetic stimulation and task performance are uncoupled in time. Such offline use of rTMS in the study of brain function and cognition is based on studies of motor cortex in which it has been shown that a continuous train of stimulation can modulate cortical excitability beyond the

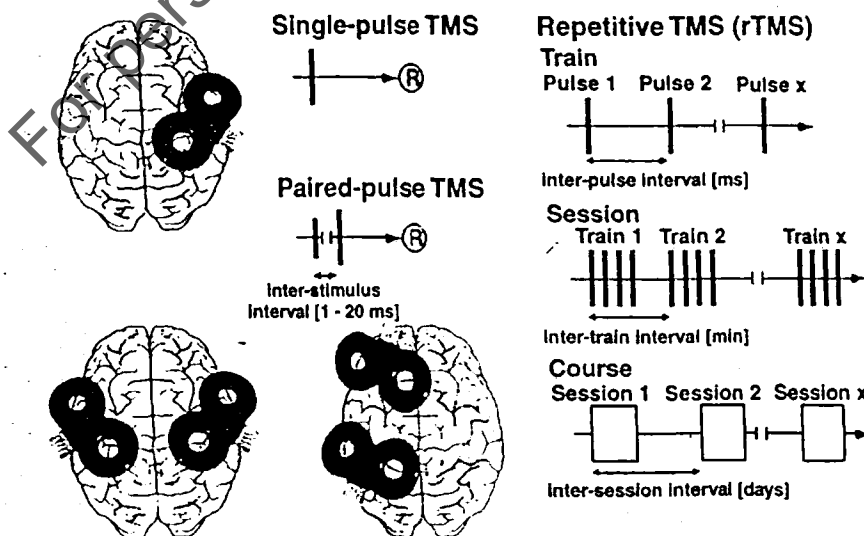


Figure 10 Schematic representation of the different ways of applying TMS: single pulse, paired pulse to a single or to two different brain areas, and repetitive (slow or rapid) TMS.

duration of the rTMS train itself (Chen *et al.*, 1997; Berardelli *et al.*, 1998; Pascual-Leone *et al.*, 1998). Depending on stimulation frequency and intensity, motor cortex excitability can either be enhanced or be reduced as measured with motor-evoked potentials (MEP) (Pascual-Leone *et al.*, 1998; Hallett *et al.*, 1999). Slow rTMS (1 Hz) applied to motor cortex can give rise to a lasting decrease in corticospinal excitability (Chen *et al.*, 1997; Maeda *et al.*, 2000a), while fast rTMS (5, 10, and 20 Hz) can induce an increase in cortical excitability (Pascual-Leone *et al.*, 1994a; Berardelli *et al.*, 1998; Maeda *et al.*, 2000a). It is, however, important to recognize the significant inter- and intraindividual variability of these modulatory effects of rTMS (Maeda *et al.*, 2000a; Fig. 11). Nevertheless, it is hypothesized that application of rTMS to cortical areas other than motor creates similar modulations (decreases or increases) in cortical excitability, which lead to measurable behavioral effects (Pascual-Leone *et al.*, 1999a). This approach has recently been implemented in a number of cognitive studies, including visual perception (Kosslyn *et al.*, 1999), spatial attention (Hilgetag *et al.*, 2001), motor learning (Robertson *et al.*, 2001), working memory (Mottaghy *et al.*, 2001), and language (Shapiro *et al.*, 2001). In addition, this capacity of rTMS of modulating cortical excitability has suggested the possibility of using TMS in therapeutic applications in neuropsychiatric conditions associated with abnormalities in

cortical excitability (Pascual-Leone *et al.*, 1998; Wasserman and Lissanby, 2001).

C. Positive and Negative Effects of TMS

TMS can have disruptive, "inhibitory" effects on perceptual or motor performance or can sometimes paradoxically improve performance. This leads to the question of whether, in its disruptive or productive modes, TMS stimulates excitatory or inhibitory neurons. If one considers the mechanisms of TMS induction (see above) it becomes readily apparent that TMS cannot be expected to distinguish between excitatory and inhibitory neurons within a region of stimulation, nor can it be expected to distinguish between orthodromic and antidromic direction of stimulation. Delivery of a TMS pulse will randomly excite neurons that lie within the effective induced electrical field. For these reasons it is best to consider TMS as operating in two ways. In its disruptive mode, TMS applied while a subject is trying to perform a task induces neural noise into the signal processing system. Just as the stimulation is likely to be random with respect to inhibition, excitation, and direction of current along any given membrane, so too can it be presumed to be random with respect to the organization of the neural assemblies involved in any particular task. There are some situations in which TMS might be considered to operate in a productive mode and add signal rather than noise, for example, in the functional enhancements produced by TMS (Walsh *et al.*, 1998; Hilgetag *et al.*, 2001) or in the production of phosphenes (Kammer, 1999; Kammer and Nussek, 1998). However, the enhancements reported by Walsh *et al.* and Hilgetag *et al.* were caused by a disruption in one area resulting in disinhibition in a competing region of cortex, and as Kammer has argued cogently, the physiological effects that produce phosphenes are identical with those that produce visual deficits.

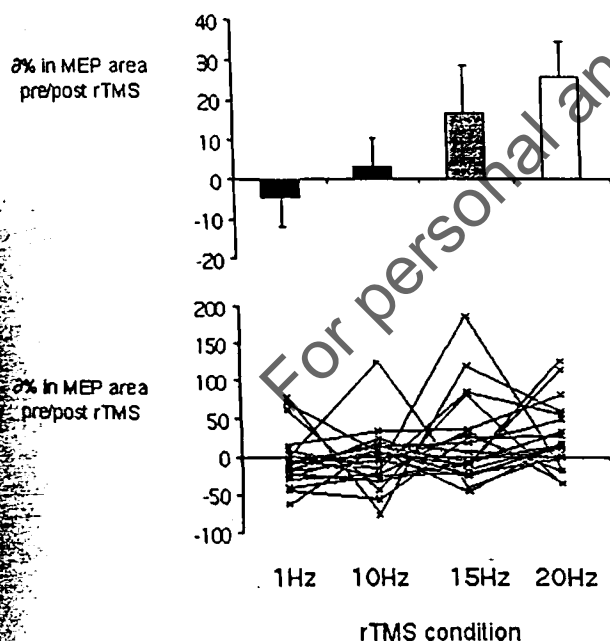


Figure 11 Modified from Maeda *et al.* (2000a,b), with permission. Frequency tuning curves for different subjects are shown. The total number of pulses applied at each rTMS condition was 240. The top shows the mean percentage changes in the averaged MEP area from pre- to post-rTMS. The bars indicate standard error. The bottom shows frequency tuning curves of each individual. Abbreviation: $\Delta\%$, percentage change.

III. TMS in Clinical Neurophysiology

When TMS is applied to the motor cortex at appropriate stimulation intensity, it is possible to record MEPs in contralateral extremity muscles (Fig. 12). If the stimulation coil is placed over the spinal column such that nerve roots are stimulated, a radicularly induced MEP can be recorded. The latency difference between the MEP induced by cortical stimulation and the one evoked by radicular activation provides a measure of central motor conduction time (CMCT). Alternatively, the latency of an H reflex of the F wave can be used to obtain more precise measurements of peripheral latency and hence obtain more accurate measures of CMCT. Rossini and Rossi (1998), Rothwell (1997), and Mills (1999) have provided recent reviews on the clinical utility of CMCT determinations.

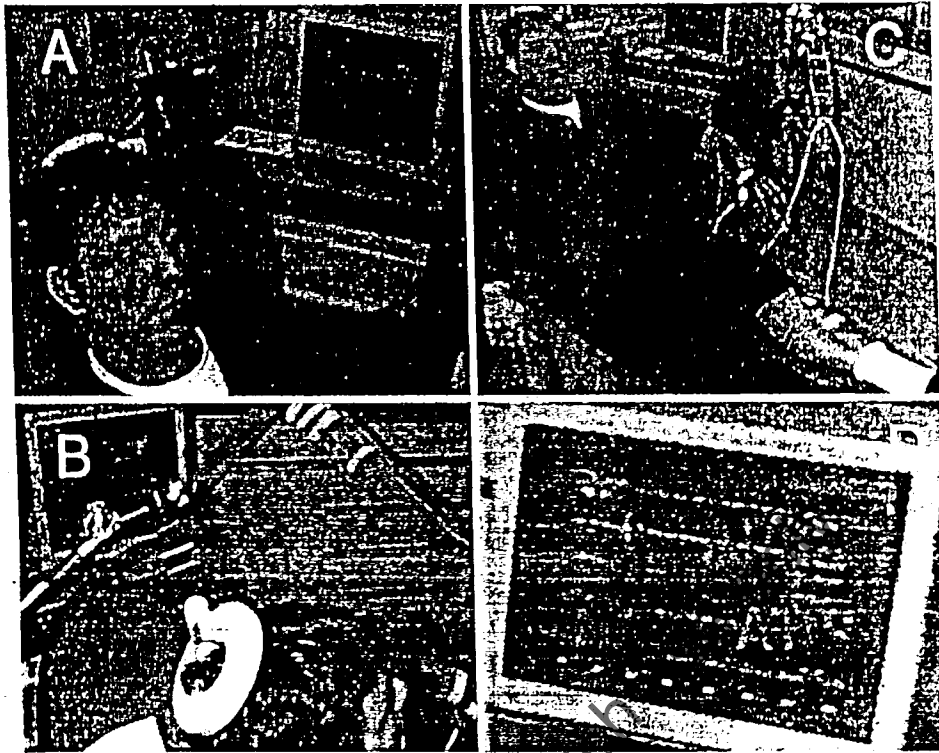


Figure 12 Composite of photographs illustrating the experimental setup for recording of motor evoked potentials to TMS. Julian P. Keenan, Ph.D., demonstrates as a pretend subject for a study. Stimulation is applied transcranially with a circular coil resting on the subject's head and targeting the motor cortex (A and B). The stimulation coil is held in place by a specially designed coil holder (A and B). Surface electrodes are used to record simultaneously the EMG activity in the abductor pollicis brevis (APB) and the anterior tibialis (C and D). EMG activity and evoked motor potentials are recorded and analyzed using a commercially available EMG device (depicted is the Counterpoint by Dantec Medical, Denmark).

A. Measures of Cortical and Corticospinal Excitability

If TMS is applied to the motor cortex, different TMS paradigms can be used to study different components of cortical excitability and provide insight into the function of different neurotransmitter systems. Figure 13 illustrates these different measurements. Single-pulse TMS can be applied to the motor cortex to determine *motor threshold*. Motor threshold refers to the lowest TMS intensity to evoke MEPs in a target muscle in 50% of trials. Motor threshold is felt to represent a measure of membrane excitability in pyramidal neurons. Support for this claim comes from changes in motor threshold induced by antiepileptic medications with prominent sodium and calcium channel-blocking activity but limited or absent neurotransmitter interaction (carbamazepine, phenytoin, or losigamine) (Ziemann *et al.*, 1996c).

Single-pulse TMS can also be applied at suprathreshold intensity to the motor cortex to study the induced *silent period* (Fig. 13). Silent period refers to the suppression of EMG activity in the voluntarily contracted target muscle following the induction of a motor-evoked potential. Studies of seg-

mental spinal excitability during this silent period have established the cortical origin of at least the later part of the evoked EMG silence (Brasil-Neto *et al.*, 1995; Fuhr *et al.*, 1991; Schnitzler and Benecke, 1994; Triggs *et al.*, 1993; Wilson *et al.*, 1993a). This postexcitatory cortically generated inhibition can sometimes be observed in the absence of preceding facilitation (silent period without preceding MEP) (Catano *et al.*, 1997; Triggs *et al.*, 1993; Wassermann *et al.*, 1991) and can be shown to have a cortical origin distinct from the optimal site for activation of a given target muscle (Lewko *et al.*, 1996; Wassermann *et al.*, 1993; Wilson *et al.*, 1993b). The balance of cortical glutamatergic (Faig and Busse, 1996; Prout and Eisen, 1994; Yokota *et al.*, 1996), dopaminergic (Priori *et al.*, 1994; Ziemann *et al.*, 1996a), and GABAergic activity (Inghilleri *et al.*, 1993; Nakamura *et al.*, 1997; Ziemann *et al.*, 1995, 1996b,c) seems to play a critical role in the duration of the silent period to TMS. Indeed, GABA-B activity may be particularly critical for the generation of the silent period. However, there is some debate about precisely when the silent period begins, how one should measure it, and what the underlying physiology is (Mills, 2000; Ziemann and Hallet, 2000). Nevertheless, several uses of the silent period

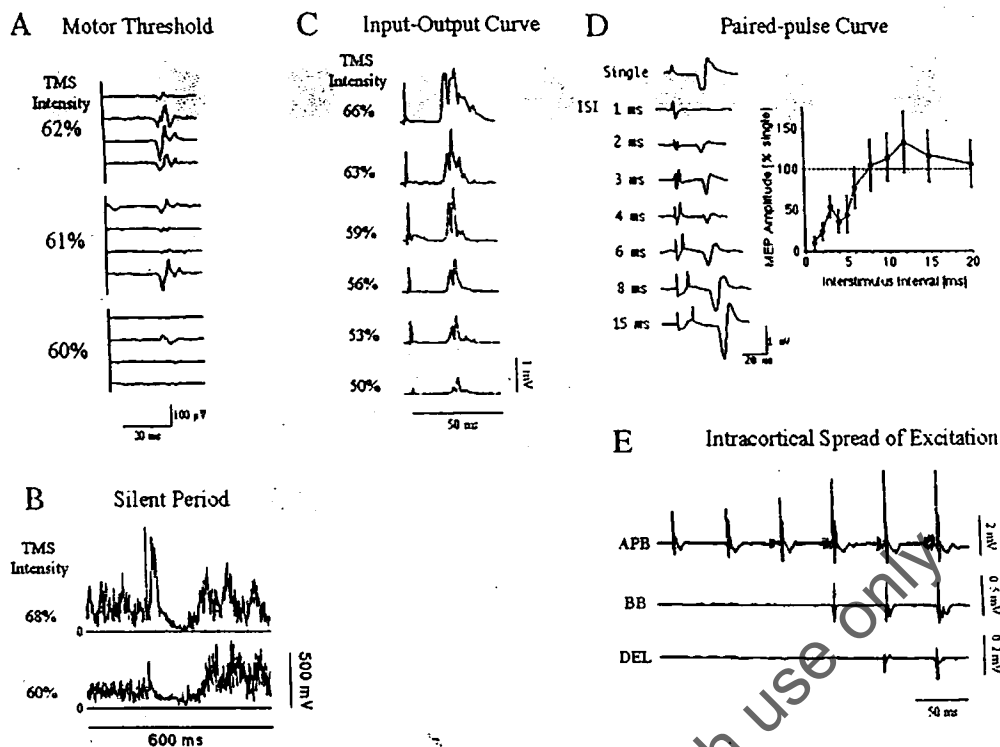


Figure 13 Modified from Pascual-Leone *et al.* (1998), with permission. (A) Representative examples of MEPs induced by TMS at decreasing intensities and recorded from the abductor pollicis brevis muscle in a normal volunteer during the determination of motor threshold. TMS intensity is expressed as a percentage of maximal stimulator output. Note that at an intensity of 62%, MEPs are induced in four of four trials. At an intensity of 61% criterion MEPs ($\geq 50 \mu$ V peak-to-peak amplitude) are recorded in only two of four trials. At 60% intensity criterion MEPs are recorded in only one of four trials. In practice, we would rely on 10 consecutively recorded MEPs rather than only on 4. (B) Representative of silent periods evoked by TMS at different stimulator output intensities in a normal volunteer. Responses are recorded from the first dorsal interosseus muscle. Note the MEP and the postexcitatory silent period at 68% TMS intensity. Note the silent period without preceding MEP at 60% intensity. (C) Examples of MEPs in an input-output curve in a normal volunteer. Rectified and averaged MEPs of a total of 15 single MEPs recorded from the thenar musculature at different stimulus intensities are shown. Note that with increasing TMS intensity there is a progressive increase in MEP amplitude and area, progressive decrease in latency, and progressive prolongation in MEP duration. (D) Paired-pulse curve to TMS in a normal volunteer recorded from the first dorsal interosseus muscle. The conditioning stimulus was applied at 80% of the subject's motor threshold intensity, while the test stimulus was applied at 115%. On the left, representative examples of the recorded MEPs are given for various interstimulus intervals (ISI). On the right, the curve of modulation of MEP amplitude depending on interstimulus interval is displayed for a normal volunteer. MEP amplitude is expressed as percentage of the average amplitude of MEPs evoked by the test stimulus alone (% of single). (E) EMG recording from the abductor pollicis brevis (APB), biceps brachii (BB), and deltoid (DEL) muscles during a train of rTMS (20 Hz, 120% motor threshold intensity) to the optimal scalp position for activation of the hand muscles. Note the progressive increase in amplitude of the MEPs in the APB and the appearance of MEPs in the BB and DEL after four and five stimuli, respectively.

seem particularly relevant. First, the silent period can be used as a marker of cortical modulation and thus changes in length or depth due to learning or disease serve as indicators of the site of damage. Second, because it is independent of previous muscle activity and can be elicited at lower levels of stimulation than MEPs, the silent period is sometimes a more sensitive measure of TMS effects than MEPs.

Single TMS pulses of progressively increasing intensity applied to the motor cortex can be used to generate an *input-output curve* (Fig. 13). The resulting modulation of amplitude of MEPs to increasing intensity of TMS pulses

appears to provide a measure of excitatory feedback to corticospinal efferent output (Valls-Sole *et al.*, 1994), which seems glutamatergically mediated (Prout and Eisen, 1994).

Intracortical excitability can be further studied using the *paired-pulse TMS technique* (Fig. 13) (Kujirai *et al.*, 1993). A first, conditioning stimulus is applied, followed, at a variable interval, by a second, test stimulus. The effects obtained depend upon the intensity of the conditioning stimulus, the interval between the stimuli, and the intensity of the test stimulus. The intensity of conditioning and test stimuli influences the effects as different circuits are recruited by different

intensities of stimulation. The interstimulus interval (ISI) influences the results as the time constant of each activated circuit may differ. At very short ISIs (<1 ms) it is possible to study neural time constants of the stimulated elements, at ISIs of 1–4 ms it is possible to investigate interactions between I-wave inputs to corticospinal neurons, and at ISIs of 1–20 ms it is possible to investigate corticocortical inhibitory and facilitatory circuits. All these effects appear to be cortically mediated (Kujirai *et al.*, 1993; Valls-Sole *et al.*, 1992; Ziemann *et al.*, 1996d) and intracortical inhibition and facilitation appear to be due to activation of separate circuits (Ziemann *et al.*, 1996d). The effects of different illnesses and medications on the inhibitory and facilitatory phases of the paired-pulse curve suggest that GABAergic and dopaminergic mechanisms are involved. Medications that enhance GABAergic activity have been shown to markedly decrease the degree of corticocortical facilitation evoked by paired TMS stimuli at ISIs of approximately 8–12 ms (Inghilleri *et al.*, 1996; Ziemann *et al.*, 1995, 1996b,c). Conversely, in Parkinson's disease, the dopamine deficiency is associated with reduced corticocortical inhibition at short ISIs (<5 ms) (Berardelli *et al.*, 1996; Ridding *et al.*, 1995), and dopaminergic drugs have been shown to enhance corticocortical inhibition in normal subjects and Parkinsonian patients (Berardelli *et al.*, 1996; Priori *et al.*, 1994; Ridding *et al.*, 1995; Ziemann *et al.*, 1996a). Furthermore, studies suggest that an early phase of facilitation in the paired-pulse curve at approximately 3 ms ISI might be related to glutamatergic, excitatory intracortical modulation (Detsch and Kochs, 1997; Prout and Eisen, 1994; Ziemann *et al.*, 1996d).

Finally, the modulation of the MEPs recorded in contralateral muscles during rTMS trains provides evidence of the pattern of reentry inhibitory and excitatory pathways (Jennum *et al.*, 1995; Pascual-Leone *et al.*, 1994c). Repetitive TMS trains at different intensities and frequencies differentially modulate MEPs. During trains of rTMS at appropriate intensity and frequency, the phenomenon of *intracortical spread of excitation* (ISE) (Fig. 13) has been described (Pascual-Leone *et al.*, 1994c). ISE appears most likely due to the breakdown of GABAergic inhibition. The number of TMS pulses until onset of ISE at a given rTMS frequency and intensity provides a measure of intracortical surround inhibition control which can be shown to be altered, for example, in patients with epilepsy.

These different measures of cortical excitability can be applied to the study of cortical pathophysiology in a variety of neuropsychiatric conditions and may in the future have a profound impact on therapeutic approaches. For example, patients with epilepsy have altered measures of intracortical excitability (Caramia *et al.*, 1996; Jennum and Winkel, 1994; Michelucci *et al.*, 1996; Reutens *et al.*, 1993) that may, in the future, allow differentiation among forms of epilepsy that cannot be predicted on clinical grounds alone. Different antiepileptic drugs, in accordance with their

known mechanisms of action, have different effects on intracortical excitability (Ziemann *et al.*, 1996c) and these effects could be used to predict which medication might be best suited to normalize the dysfunction in different patients. Nowadays, in a large number of patients with epilepsy, the choice of an antiepileptic drug for a given patient is made empirically using cost and side-effect profile as principal determinants rather than expected efficacy or mechanisms of action. TMS-derived measures of cortical excitability might in the future guide more pathophysiologically based approaches to neuropharmacology.

B. Strategies for Clinical Applications of TMS

In the present chapter we will concentrate on clinical applications of *transcranial magnetic stimulation*. However, magnetic stimulation can also offer substantial advantages over electric stimulation for the study of nerve root and spinal plexus disorders (Maccabee *et al.*, 1996) or the study of cranial nerves (Benecke *et al.*, 1998).

Most clinical applications of TMS can be performed with a single-pulse magnetic stimulator and a conventional EMG machine. A large circular coil (outer diameter of approximately 10 cm) is sufficient for all routine applications. Smaller circular coils might be required for the stimulation of the facial nerve behind the mandibular angle or the accessory nerve in the posterior fossa. Focal figure-8 coils are needed for reliable hemisphere-selective activation of the motor cortex. The stimulus intensity employed should be expressed in percentage of motor threshold intensity of the recorded muscles at rest. For induction of reliable MEPs in contralateral hand muscles intensities of approximately 120% of motor threshold are sufficient. Induction of MEPs in leg muscles might require maximal stimulator output intensities and the use of specially shaped, double-cone coils.

In general, for most diagnostic applications TMS is applied to the motor cortex and MEPs are recorded using surface electrodes taped over the belly and tendon of the target muscle(s). Frequently, in order to fully interpret the results, motor cortex TMS has to be combined with peripheral nerve, nerve plexus, or spinal root stimulation. As is the case in EMG, the specific sites of stimulation, the recorded muscles, the maneuvers used for facilitation of the motor-evoked potentials, and the evaluation of the different response parameters have to be tailored to the specific questions asked. The following four examples illustrate possible approaches.

(1) In a patient suspected of having a hysterical hemiparesis, TMS can be applied to the motor cortex and MEPs recorded from several arm and leg muscles bilaterally. All target muscles should be relaxed to allow side-to-side comparison of MEPs elicited under similar conditions. A circular TMS coil is most suited to such an application. MEPs of similar amplitude in both hemibodies usually exclude an

organic cause of the hemiparesis, provided that a motor hemineglect and lesions in supplementary or premotor cortical areas are excluded.

(2) In a patient with a suspected spinal cord lesion, TMS is applied to the motor cortex and the MEPs are recorded using surface electrodes from an intrinsic hand muscle (e.g., abductor pollicis brevis or first dorsal interosseus) and a distal leg muscle (e.g., anterior tibial muscle). The comparison of the responses in upper and lower extremities will help define the level of the spinal lesion. The tonic contraction of the target muscles facilitates the spinal motoneurons, thus increasing the likelihood of MEP recording and minimizing conduction velocity. Since it might be difficult to detect small MEPs in contracted muscles and determine their latency, it is useful to rectify and average several responses. In paraplegic patients, electrical stimulation of peripheral nerves to elicit an H reflex or sensory stimuli to elicit a flexor or a Babinski reflex might be used to facilitate spinal leg motoneurons further. MEPs to motor cortex TMS can also be recorded from paravertebral muscles using needle electrodes to define the exact level of the spinal cord lesion more precisely (Meyer *et al.*, 1998a).

(3) In a patient with the clinical picture of motor neuron disease an early diagnosis can be difficult and yet prognostically important as new therapeutic options become available. TMS is applied to the motor cortex and MEPs are recorded from several upper and lower extremity muscles. The target muscles might need to be tonically contracted to facilitate the responses. Rectification and averaging of the EMG responses is useful given the small amplitude of the expected MEPs. H reflexes or magnetic stimulation of the spinal roots can be used for determination of the peripheral nerve conduction. Central motor conduction time is calculated by subtracting this peripheral conduction time from the latency of the TMS response. Central conduction time is prolonged in motor neuron diseases due to the loss of corticospinal cells (Eisen *et al.*, 1990). In addition, the contralateral silent period to motor cortex TMS is significantly briefer than normal. Careful determination of the motor threshold is particularly important in this context as it might help differentiate between amyotrophic and primary lateral sclerosis (Carania *et al.*, 1997; Eisen *et al.*, 1993). Patients with the former condition have lower than normal motor thresholds, while those with the latter show significantly increased motor thresholds.

(4) In a patient with the suspected diagnosis of multiple sclerosis, TMS is applied to the motor cortex bilaterally using a circular coil and MEPs should be recorded from at least four muscles, ideally bilaterally from two hand and two lower limb muscles. In addition to the mean values of MEP latency and amplitude (Rossini and Rossi, 1998), the variability of both parameters should be carefully considered as a further indicator of impaired corticospinal conduction (Britton *et al.*, 1991).

Measurements of *transcallosal inhibition* might demonstrate a disruption of callosal fibers by periventricular foci even in patients with normal corticospinal responses (Meyer *et al.*, 1995). In addition, such demonstration of transcallosal fiber dysfunction is likely to have prognostic relevance for the cognitive consequences of the multiple sclerosis. For this purpose, TMS is applied to the motor cortex while EMG responses are recorded in tonically contracted ipsilateral hand muscles. In response to the TMS there is a transient suppression of tonic EMG activity due to the transcallosal inhibition of the unstimulated motor cortex (Meyer *et al.*, 1995, 1998a). Several EMG responses are rectified and averaged. Latency, duration, and degree of the transcallosal inhibition can be measured. The latency is defined as the time between the cortical stimulus and the point at which the EMG activity falls under the mean amplitude of the EMG activity before the stimulus. The duration spans between the onset of transcallosal inhibition and the point at which the EMG activity again reaches the mean amplitude of the baseline EMG activity before the stimulus. The degree of EMG suppression is calculated as the percentage decrease of the baseline EMG amplitude before stimulation.

These examples emphasize the notion that diagnostic TMS cannot follow rigid guidelines. Careful thought has to be given to ensure that the number of recorded muscles is sufficient, adequate processing of the responses is performed offline, and suitable facilitation procedures are employed.

There are certainly other important clinical uses of TMS. For example, TMS can help (1) to distinguish between a predominantly demyelinating and an axonal lesion in the descending motor tracts; (2) to detect the level of a hemispheric lesion in relation to the course of transcallosal fibers; (3) to help predict the motor outcome after a vascular cerebral lesion; or (4) to obtain objective data to evaluate the progression of a disease (e.g., myelopathy) or the effects of treatment (e.g., in transverse myelitis). Furthermore, magnetic stimulation can be used for intraoperative monitoring of corticospinal motor tract function during spinal surgery in order to optimize surgical outcomes (Herdman *et al.*, 1993).

C. Mapping Motor Cortical Outputs

TMS can be applied sequentially to different scalp positions as the evoked response from each site of stimulation is recorded, hence generating a spatial map of behavioral manifestations (Hallett, 1996; Walsh, 1998). Most commonly, TMS mapping is applied to motor cortical output and uses the amplitude or the area under the curve of the MEPs as the measure of the motor response (Brasil-Neto *et al.*, 1992a; Thickbroom *et al.*, 1998; Wassermann *et al.*, 1992; Wilson *et al.*, 1993a). However, other neurophysiologic markers or behavioral manifestations, such as the direction of induced finger movements or the performance in a given cognitive

task (Wassermann *et al.*, 1998), could be used and "mapped" in the same manner. This type of application of TMS might provide a method for noninvasive, systematic assessment of cortical function in the presurgical planning of neurosurgical procedures. The advantage of TMS over other brain mapping methods, particularly current functional imaging methods, is that it can provide information about true functional significance of the brain area targeted (Krings *et al.*, 1997a). Therefore, the neurosurgeon can be told, not just that a given brain region in some way participates or is associated with a given behavior, but indeed what the consequences will be if that part of the brain is damaged during the surgical procedure. Being able to provide this kind of information would be obviously desirable (Cramer and Bastings, 2000; Krings *et al.*, 1997a). However, work is still needed to fulfill this clinical potential. For example, it is imperative to establish a method of reliably transferring scalp positions (over which TMS is applied) to brain cortical sites (Miranda *et al.*, 1997). Frameless stereotactic methods might be the solution to this problem, but they do not fully address the question of field distribution of the TMS in a real brain (Bohning *et al.*, 1997). Factors like cerebrospinal fluid space, which by virtue of its much greater conductivity compared to brain tissue can significantly distort the electromagnetically induced currents in TMS and hence shift the site of brain stimulation from the strict perpendicular projection of the scalp position of the coil, need to be fully explored. Careful studies correlating the results of TMS and direct cortical stimulation mapping procedures are needed and have only begun to be done for the motor cortex (Krings *et al.*, 1997b, 1998). Similar studies for language representation and other "eloquent" cortical regions are still needed in order to assess the clinical significance of TMS for this purpose.

In research, TMS mapping has proven a valuable tool for exploring issues of plasticity in the adaptation to injury and the acquisition of new skills (Cohen *et al.*, 1998; Pascual-Leone *et al.*, 1999a). Expansion of a specialized cortical area and recruitment of a remote area as a result of learning or brain disease or injury comprise the two most characteristic forms of brain plasticity. The underlying general phenomenon is that neurons in one area assume properties of neurons in an adjacent or remote area. Such remodeling can take place across brain areas within a given modality, for example, within visual, tactile, or motor distributed systems (homotypic or intramodal plasticity), or may bridge across modalities (heterotypic or cross-modal plasticity), as in the case of tactile information processing in the occipital ("visual") cortex in the blind (Cohen *et al.*, 1997; Sadato *et al.*, 1996, 1998). The time course of plasticity is extended, with some changes appearing within seconds of the initial event and continuing many years after an intervention or injury. TMS can be used in this setting to demonstrate plastic changes and to serially track them in time.

Several studies can serve to illustrate this type of application of TMS mapping. Pascual-Leone *et al.* studied how the motor cortical output maps change in normal subjects as they learn to perform with one hand a five-finger exercise on a piano keyboard (Pascual-Leone *et al.*, 1995) and how implicit and explicit knowledge of a sequence influences motor cortical maps during a procedural learning task (Pascual-Leone *et al.*, 1994a). It is important to realize that such serial TMS mapping studies demonstrate a trace or memory of the activation of the motor cortical outputs that took place during the performance of a task rather than the activation during the task itself as would be the case with neuroimaging studies. Therefore, such TMS mapping studies might be revealing the consequences of long-term potentiation or long-term depression on cortical function (Butefisch *et al.*, 2000; Classen *et al.*, 1998) and longer lasting and slower mechanisms of plasticity such as sprouting and establishment of new connections.

In the setting of adjustment of injury, serial TMS mapping following a stroke (Cramer and Bastings, 2000; Rossini *et al.*, 1998) promises to aid our understanding of the mechanisms involved in the recovery of function after a brain lesion and might provide insight into new therapeutic and neurorehabilitation approaches (Liepert *et al.*, 2000). The study of cortical plasticity after amputation provides another clear example of the utility of TMS mapping (Chen *et al.*, 1998; Cohen *et al.*, 1991a). Pascual-Leone *et al.* (1996) tracked the changes in motor cortex excitability from months before to months after a subject lost his right hand and arm and forearm. In the year following the amputation the motor output maps of the amputated biceps and lower facial muscle ipsilateral to the amputated arm expanded over the original representation of the right hand. The expansion was associated with disappearance of phantom sensations and also with the disappearance of the ability of TMS to elicit phantom experience. Figure 14 shows the progressive changes in the area over which EMG responses can be elicited and the gradual diminution of phantom responses.

D. Development and Maturation

Serial studies of cortical excitability (motor threshold, silent period, paired-pulse curves, input-output curves) and TMS mapping can be used for the study of nervous system development and maturation. The development of motor coordination continues throughout childhood and into adolescence and one of the problems the nervous system has to solve is how to maintain motor control over a period of life during which an individual may grow from one-half to two meters and during which the rate of that growth may vary over a 20-fold range. Not only is the child growing in height but the limbs are growing and the area swept by any movements changes as a result. One proposed solution is that the nervous system employs constant conduction times

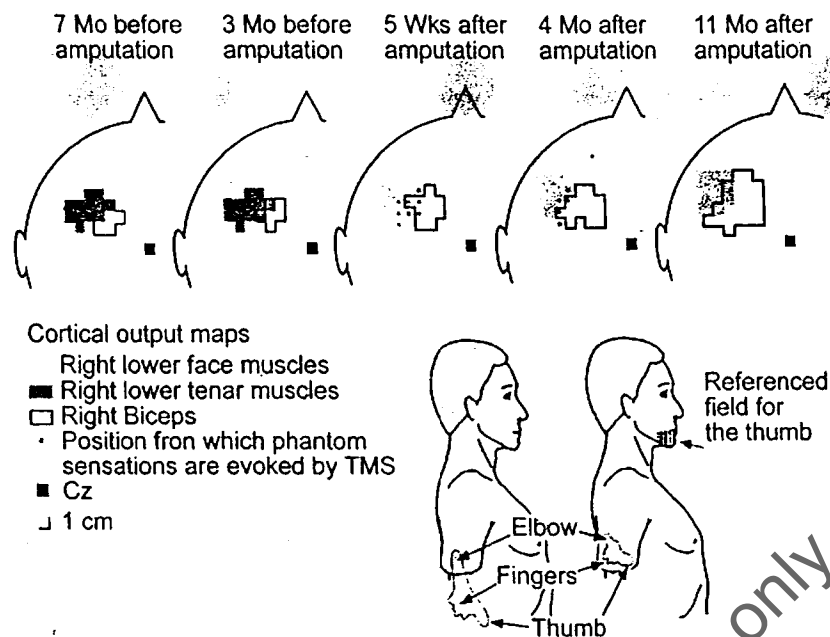


Figure 14 Serial TMS maps in a subject who suffered a traumatic amputation of the right arm. Reproduced from Pascual-Leone *et al.* (1996), with permission.

rather than a more complex mechanism that would be able to track changing timing requirements throughout development. Eyre *et al.* (1991) tested this possibility directly by measuring conduction times and sensitivity to TMS (in the form of MEP threshold) in over 400 subjects between the ages of 32 weeks and 52 years. They applied TMS over the motor cortex and the cervical spine and recorded EMG from the biceps and the hypothenar muscles. They found that cortical-evoked MEPs decreased in latency from 32 weeks until approximately 2 years of age and then plateaued at adult levels. The latencies of response following cervical stimulation were relatively constant until 4–5 years of age and thereafter increased in proportion to arm length across all ages. The motor threshold also decreased markedly over time until approximately 16 years of age. Müller *et al.* (1997) have extended this type of longitudinal, developmental study to the investigation of the ipsilateral corticospinal pathways, and Heinen *et al.* (1998) have explored the question of the relation between motor skills and corticospinal conduction velocity. Future studies should be able to similarly explore developmental questions in nonmotor systems and provide insight into the correlation of longitudinal neurophysiologic changes and the development of symptoms and diseases, such as dyslexia or gait disturbance in cerebral palsy.

E. Potential Future Clinical Uses of TMS

The development of special techniques offers the opportunity of widening the clinical uses of TMS. We have

already introduced paired-pulse TMS techniques that can be used to study intracortical excitability. As discussed above, in addition to diagnostic applications in diseases such as dystonia or obsessive-compulsive disorder, paired-pulse TMS could provide neurophysiologic measurements to guide pharmacological interventions. Repetitive TMS can be used in the study of higher cortical functions, and clinically it might be particularly useful for the noninvasive determination of the language-dominant hemisphere (Epstein, 1998). Interference with language comprehension by single-pulse TMS is quite subtle. However, rapid stimulation over the frontotemporal area can produce prominent impairment of speech output. In series reported thus far, success at inducing complete speech arrest has been possible in approximately 75% of the subjects studied with rTMS applied at frequencies ranging from 4 to 30 Hz. Two studies on epileptic patients who had undergone intracarotid amobarbital (Wada) tests found a concordance with the rTMS effects of 100% (Pascual-Leone *et al.*, 1991) and 95% (Jennum *et al.* 1994). However, careful studies in normal subjects have noted that rTMS might overdiagnose atypical language representation (Epstein *et al.*, 1996a, 1996b, 1998). In addition, the speech deficits induced by rTMS may represent anarthria and dysarthria more frequently than aphasia and be primarily due to disruption of the laryngeal or facial motor outputs (Epstein, 1998). Finally, rTMS over the temporalis muscle in order to target lower frontal cortex can be uncomfortable due to associated facial twitching and pain. Therefore, the clinical application of rTMS for determination of the speech-dominant hemisphere requires

further investigation. Its sensitivity and specificity for language lateralization require further verification before it can supplant better-established procedures such as the intracarotid amobarbital test.

Image-guided frameless stereotactic techniques provide a method for precise localization of the brain region targeted by TMS applied to the scalp (Paus, 1999). A subject's brain MRI can be used to identify the anatomical substrate for the TMS effects. In this fashion, the location of the motor cortex in relation to a patient's brain lesion can be precisely identified noninvasively (Krings *et al.*, 1997b, 1998). In addition, functional neuroimaging studies can be used to guide the target of TMS, which would then be able to provide causal information about the behavioral significance of the measured brain activity. For example, functional MRI studies might reveal several areas of activity when a patient talks or moves a finger. TMS can sequentially target these different areas of activation of the fMRI and selectively and transiently disrupt their function, creating "transient lesions." This approach will provide the neurosurgeon with invaluable information regarding the likely consequences of damage to different brain areas. Therefore, in patients being evaluated for neurosurgical procedures, such information would allow timely planning of the intervention and would likely reduce complications. Nevertheless, at this point, further research is required to test the clinical utility of such TMS applications.

As mentioned above, the capacity of rTMS for modulating cortical excitability has suggested the possibility of using TMS in *therapeutic applications in neuropsychiatric conditions* associated with abnormalities in cortical excitability (Pascual-Leone *et al.*, 1998; Wasserman and Lissanby, 2001). As reviewed by Wasserman and Lissanby, the therapeutic applications of rTMS in diseases such as depression, schizophrenia, acute mania, obsessive-compulsive disorder, focal dystonia, Parkinson's disease, tremor, myoclonus, or epilepsy are potentially exciting, but remain highly preliminary and it would be premature to consider them of established clinical significance at this point.

IV. TMS in Cognitive Neuroscience

A. Creating Virtual Patients

The development of TMS in cognitive neuroscience has been mainly due to the ability of TMS to enhance the lesion analysis approach to psychology by temporarily disrupting sensory or cognitive processes. Single TMS pulses disrupt activity for only some tens of milliseconds and provide information on *when* activity contributes essentially to task performance (the "chronometry" of cognition). Normal cognitive processes can thus be probed with TMS by the creation of "virtual lesions," which offer numerous advantages

over the classical neuropsychological approach of inferring brain function from the behavior of brain-lesioned patients. The use of normal subjects in TMS studies removes the possible confounds of size of lesion, general cognitive impairments resulting from the brain injury, and plastic brain reorganization after the insult. In addition, the same subjects can be tested repeatedly while the same paradigm can be applied to multiple participants.

Whereas single-pulse TMS can be viewed as an "online" paradigm (stimulation occurs *during* task performance), rTMS offers the advantage of an "offline" paradigm in which magnetic stimulation and task performance are uncoupled in time. Such offline use of rTMS is based on the fact that a continuous train of stimulation can modulate cortical excitability beyond the duration of the rTMS train itself and increase it or decrease it depending on rTMS frequency and intensity (Pascual-Leone *et al.*, 1998).

B. Single-Pulse Stimulation and Neurochronometry

Amassian and colleagues (1989) were the first to use TMS as a virtual lesion technique in the visual system and also the first to extend this to probe the cortical basis of the well-established psychological phenomenon of visual masking (Amassian *et al.*, 1993a,b). In the first experiment subjects were presented with small, low-contrast trigrams and required to identify the three letters. TMS was applied using a round coil with the lower edge approximately 2 cm aboveinion. Pulses were given once per trial at a visual stimulus-TMS onset asynchrony of between 0 and 200 ms. Figure 15 shows that TMS was effective in abolishing the subjects' ability to identify the letter if the pulse was delivered between 80 and 100 ms after onset of the visual stimuli. They also demonstrated the retinotopic specificity of the effect by moving the coil slightly to the left, causing a decrease in identifying only letters on the right of the trigram, or to the right, causing a corresponding decrease in

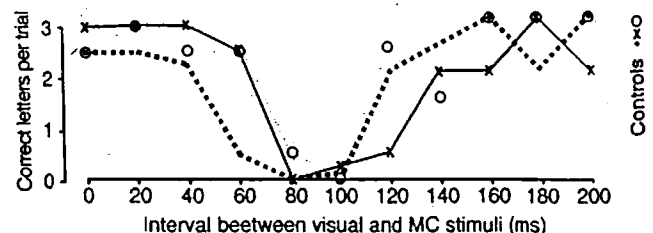


Figure 15 Visual suppression curves of three subjects. The proportion of correct identifications of three briefly flashed dark letters on a light background is plotted as a function of the delay between stimulus onset and the application of TMS pulse over occipital visual cortex. The magnetic stimulation was delivered with a round coil. Reproduced from Amassian *et al.* (1989), with permission.

identifying letters to the left. They also used vertical trigrams and showed that moving the coil dorsally disrupted perception of the lower letter and moving ventrally interrupted reports of the upper letters.

To make a real test of the specificity of the technique they needed to exclude the possibility that TMS had not made subjects worse on the task because of nonspecific effects on vision. To demonstrate that TMS was having specific effects it should be possible to find an example of two competing stimulus loads and to use TMS to selectively disrupt one in order to unmask the other. They used a classical visual masking paradigm in which subjects were presented with an initial trigram of target letters followed 100 ms later by a second set of masking letters. Following this second set of letters TMS could be applied at a trigram-TMS onset asynchrony of 0–200 ms (Fig. 16). Clearly the presentation of the second set of letters masks the processing of the first, presumably due to some overlapping time period during which initial processing of the second set prevents access to the results of processing the first set. When TMS was applied over the occipital cortex, however, the effects of the second set of stimuli were removed. TMS masked processing of the second set to unmask processing of the first and the time course of the TMS unmasking effect mirrored that of the original masking effect (Fig. 16).

Amassian's work is a good example of how to fuse TMS with psychological models and it laid the foundation for other visual TMS studies, but questions remained. For example, occipital pole stimulation may include several visual areas so other experiments are required to better define the neuroanatomical substrate of the results. The optimal latency of the TMS effect on suppression and masking (80–100 ms) led Amassian *et al.* to suggest that the critical site of stimulation lay beyond the striate cortex because neurons there can respond with shorter latencies. Cortout

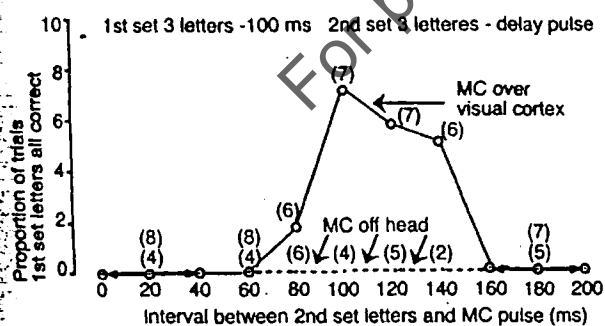


Figure 16 Masking of the first trigram produced by the presentation of a second trigram can be unmasked by TMS suppression of the second trigram. The proportion of trials in which the subjects correctly reported all the letters of the first trigram is presented as a function of the delay between the presentation of the second trigram and the TMS pulse. Numbers in parentheses are the *n* of trials with TMS (top) and with sham TMS (bottom). Reproduced from Amassian *et al.* (1993b), with permission.

et al. (1999a) have disrupted identification of centrally presented letter targets with occipital stimulation as early as 20 ms after stimulus onset, consistent with some reports from single-unit physiology (Wilson *et al.*, 1983; Schmolesky *et al.*, 1998; Celebrini *et al.*, 1993). However, late effective stimulation times may not always mean that higher levels of the visual system are being disrupted and it would not be difficult to launch the counterexplanation that late effects of TMS may be due to disruption of back projections to V1 rather than to disruption of extrastriate areas. Equating TMS time with cortical stage of processing demands corroborating evidence such as supporting single-unit physiology or knowledge of anatomical connections.

C. Virtual Patients: More than "Just" Patients

Modeling neurological patients by transient disruption of focal brain areas with TMS allows the study of brain-behavior relationships avoiding the whim and limitations of natural lesions (Pascual-Leone *et al.*, 1999a). Replicating the effects seen in patients is a good starting point for a TMS study, but it may also be a good end point. Replication is rarely exact and the differences between real and the virtual patients can be important. The work carried out with TMS on visual search and the role of the parietal cortex provides good illustration for this notion. Patients with damage to the right parietal cortex may exhibit a range of deficits that include detection of a conjunction target in a visual search array (Friedman-Hill *et al.*, 1995; Arguin *et al.*, 1990, 1993), inability to attend to the left side of visual space (Bisiach *et al.*, 1990, 1994, 1996; Bisiach and Vallar, 1988; Weintraub and Mesulam, 1987), and inaccurate saccadic eye movements. The first two deficits are often linked together and one explanation of these patients' failure to detect conjunction targets is that their spatial attentional problems prevent them from performing what is referred to as "visual binding" (Treisman, 1996). The posterior parietal cortex lies on the dorsolateral surface of the cortex and is easily accessible to TMS. In an attempt to model the effects of right parietal lesions a number of single-pulse studies have been carried out. Ashbridge *et al.* (1997) stimulated right posterior parietal cortex (PPC) while subjects carried out standard "feature" and "conjunction" visual search tasks. Patients with right PPC lesions are impaired on the conjunction tasks but not the feature tasks. TMS over right PPC replicated these two basic findings but with some important differences. Single pulses of TMS were applied at stimulus-TMS onset asynchronies of between 0 and 200 ms and subjects showed two patterns of effect. The reaction time to report "target present" was maximally increased when TMS was applied around 100 ms after visual stimulus onset but to increase the time taken to report "target absent" TMS had to be applied around 160 ms after visual array onset (Fig. 17).

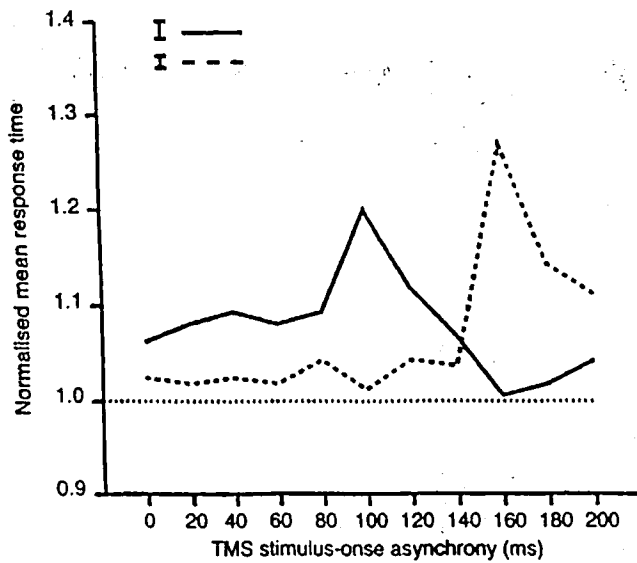


Figure 17 The effects of TMS applied over the right posterior parietal cortex of naïve subjects on a conjunction visual search task (with eight stimuli in the array). Data are normalized to the reaction time on trials when search was performed without TMS. There is a clear effect of TMS on trials when the target was present if the pulse was delivered 100 ms after stimulus onset and also when the target was absent if the pulse was delivered 160 ms after target onset. Solid lines, target present; broken lines, target absent. Vertical bars represent ± 1 standard error. Reproduced from Walsh *et al.* (1998), with permission.

Here, then, TMS has replicated the patient data (PPC damage impairs conjunction search) but it adds two further items of information—that the PPC is important for target absent responses and that the mechanisms underlying target present and target absent responses occupy different time windows in PPC. Neuropsychological patients often have an array of problems, which means that standard psychological experimental paradigms have to be modified and reaction time studies might be problematic. TMS provides a means of eliminating such potential confounds. Virtual lesions provide a controlled way to design an experiment such that multiple subjects can be tested on the same paradigm, the contribution of different brain regions to a given behavior can be evaluated, and the role of a given brain area in various behaviors can be assessed. It becomes therefore possible not only to model and reproduce, but also to extend patients' results.

D. Repetitive Pulse Stimulation

The utility of TMS does not reside only in single-pulse neurochronometric studies. If there is no temporal hypothesis under investigation, or a wide temporal window of interest, repetitive-pulse TMS can be used to disrupt behavior. Speech is a subject area in which repetitive-pulse TMS has been particularly valuable to date and illustrates the potential for future development.

One of the most dramatic demonstrations of TMS is magnetically induced speech arrest and several groups have now reported that rTMS over left frontal or either motor cortex can cause subjects to cease speaking or to stutter or repeat segments of words. As far as the neuropsychologist is concerned, this work is preliminary, no more than a calibration experiment in fact, because the emphasis has been on localizing the site of stimulation and/or establishing the most reliable parameters for speech arrest. Similarly, as discussed above, for a clinical application in the presurgical evaluation of patients, more work is required.

Pascual-Leone *et al.* (1991) were the first to induce speech arrest (25-Hz rTMS with a round coil) in a population of epileptic subjects awaiting surgery, and the TMS determination of the dominant hemisphere in all six subjects matched that obtained in the Wada test. The effect was replicated, again in epileptic patients, by Jennum *et al.* (1994; 30-Hz rTMS), whose data also showed a strong concordance with the results of the amobarbital test. The motivation for this and other early experiments on speech was the possibility that TMS could be used to replace the invasive Wada test. In studies which may require hundreds of trials, 25- and 30-Hz frequencies are too high, but a later study by Epstein and colleagues (1996a) identified 4–8 Hz as the optimum range for induction of speech arrest by TMS in normal subjects. They were also able to distinguish between arrest associated with frontal cortex stimulation, and in the absence of apparent effects on facial muscles, and effects associated with loss of control of the facial muscles. There have been some attempts to examine language functions beyond demonstrations of speech arrest but the best of these have not tested a theoretical prediction and can really be considered as further examples of generalized speech effects. Flitman *et al.* (1998), for example, applied rTMS over frontal and parietal lobes while subjects judged whether a word was congruent with a simultaneously presented picture. Subjects were slower to verify the congruency with TMS but it is not clear whether they were impaired on any particular cognitive aspect of this task or simply that the load on the language system was greater than in the control condition of stating whether the word and picture were surrounded by a rectangular frame.

Three recent studies (Epstein *et al.*, 1999; Bartres-Faz *et al.*, 1999; Stewart *et al.*, 2001a) mark the end of this 10-year period of trying to ascertain the location and reliability of speech arrest effect in normal subjects. All three studies obtained speech arrest lateralized to the left hemisphere with frontal stimulation. Epstein *et al.* suggest that their effects are due to motor cortex stimulation but this is difficult to reconcile with the left unilateral dominance of the effects and also with Bartres-Faz *et al.* and Stewart *et al.*, who provide independent anatomical and physiological evidence of a dissociation between frontal stimulation and pure motor effects (Fig. 18). Bartres-Faz and Stewart's studies both locate the critical site of stimulation to be over

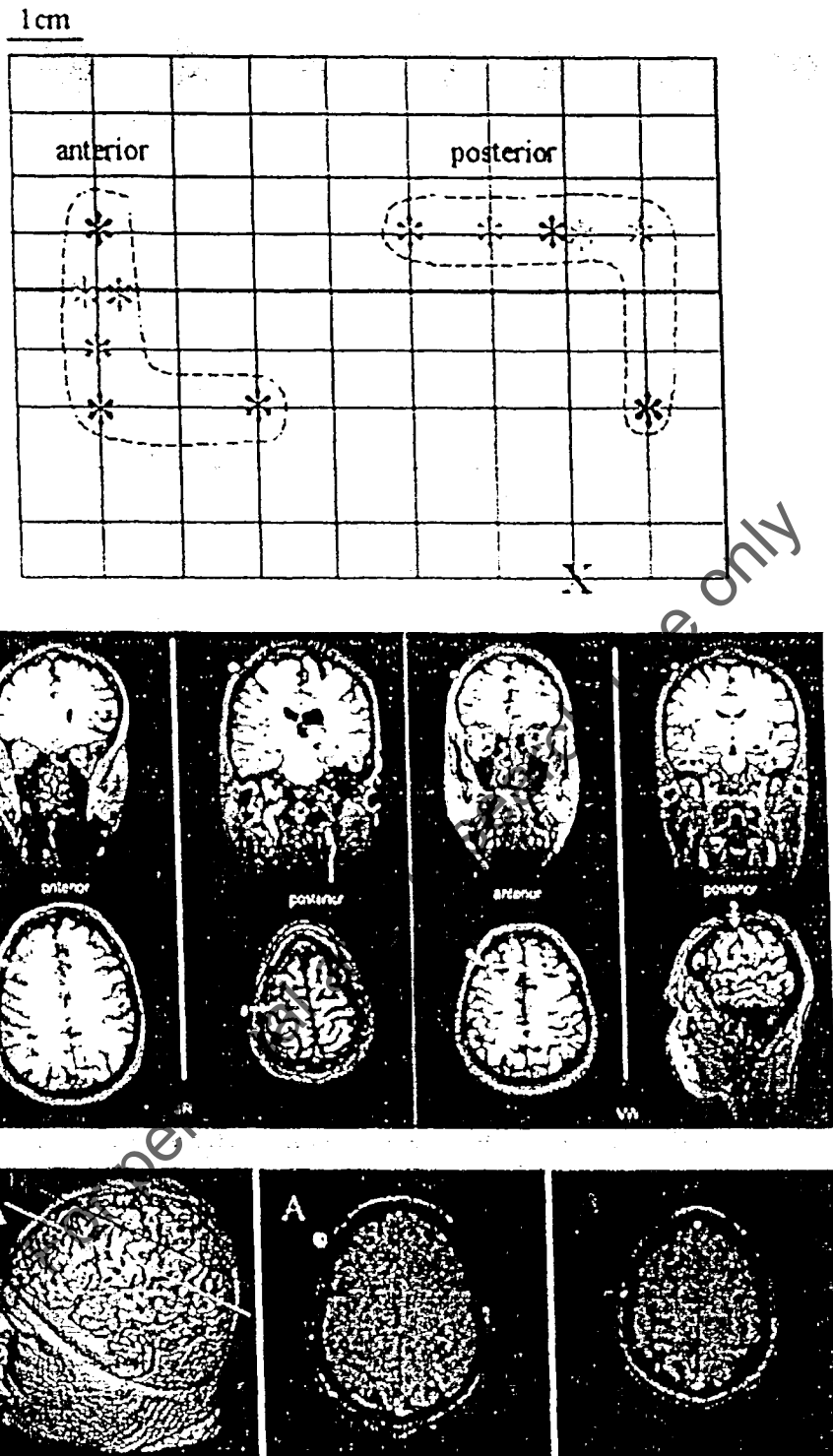


Figure 18 Modified from Stewart *et al.* (2001a), with permission. Top: Asterisks represent the areas that, when stimulated with TMS, produced speech arrest. Stimulation of the anterior site did not produce EMG activity while the posterior site was associated with mentalis muscle activity. Middle: Anatomical MRI showing the anterior and posterior sites that produce speech arrest. Bottom: Modified from Bartres-Faz *et al.* (1999), with permission. The results in a representative subject are presented. The 3D reconstruction of the subject's head MRI (left) demonstrated the sites of TMS application and the level of the axial slices of fMRI displayed in the other two panels. The middle illustrates the statistically significant fMRI BOLD changes observed during the performance of the verbal fluency task and marks on the scalp the location of the TMS coil for induction of speech arrest. Note that speech arrest is induced by TMS over brain regions that are activated during the verbal fluency task. The right side shows the most representative slice of fMRI BOLD activity corresponding to a motor task consisting of opening and closing the right hand, which is shown to be directly under the TMS scalp position that evokes hand movements (but does not lead to speech arrest). Note that the changes corresponding to the motor areas appear more posterior than those responsible for the word generation task. The latter include the areas targeted by rTMS during speech arrest.

the middle frontal gyrus, dorsal to the inferior frontal gyrus and what is usually referred to as Broca's area. These two studies are in agreement with lesion data (e.g., Rostomily *et al.*, 1991), electrical stimulation mapping (Penfield and Roberts, 1959; Ojemann and Mateer, 1979; Ojeman, 1983), and PET studies (Ingvar, 1983) that have all shown the several areas, including the middle temporal gyrus, to be important in speech production.

Speech arrest can be obtained from direct electrical stimulation of so many brain regions that it will clearly be very difficult to try to pin down a single area with TMS. The right strategy would seem to be to use TMS to produce language-related dissociations that address theoretical questions. This area is wide open for new approaches using TMS: human lesions that produce language deficits are typically large; animal lesions of course cannot address the question of language. To make use of the localization of speech arrest sites it is not necessary to induce such salient effects on every trial, and we anticipate that the typical neuropsychology experiment will be based on stimulation at intensity levels too low to induce arrest but sufficient to incur reaction time costs in verbal tasks. Stewart *et al.* (2000), for example, have begun to probe parts of the language system by taking the predictions that BA37 has a role in phonological retrieval and object naming. Repetitive-pulse TMS was applied over the posterior region of BA37 of the left and right hemispheres and over the vertex. The rTMS had significant effects on picture naming but no effect on word reading, nonword reading, or color naming. Thus, with respect to object encoding and naming, the posterior region of BA37 would seem to be critical for recognition.

Picture naming was also examined by Topper *et al.* (1998), who applied single-pulse TMS over Wernicke's area and motor cortex. Somewhat paradoxically, TMS over Wernicke's area 500–1000 ms prior to picture presentation resulted in faster reaction times than control trials. The effect was specific to task and area, and Topper *et al.* conclude that TMS "is able to facilitate lexical processes due to a general preactivation of language-related neuronal networks when delivered over Wernicke's area." While these effects are intriguing, they raise several questions about why single-pulse TMS would have facilitatory effects within a system. If generalized arousal within the language system were a tenable explanation, one would have to predict similarly modulated gains whenever TMS was applied over a language-related area. This seems unlikely to be the case. More than in any other kind of result, it is important that the apparently facilitatory effects of TMS are grounded in theoretical frameworks and that the mechanisms proposed in one modality are applicable to others. If, for example, TMS over Wernicke's area facilitates picture naming, then similar facilitations should be obtainable in other modalities. That is to say, if single-pulse TMS over one area facilitates performance in one domain, it should also do so in another. To

argue otherwise would go against the physiological similarity of neurons between areas. It is also puzzling that lower intensity TMS produced larger facilitation effects than higher intensity TMS in this study. Further studies of these effects are clearly necessary, but perhaps before basing any further conclusions on a direct facilitation, one should await evidence that an area's primary function can be disabled by TMS.

E. Paired-Pulse TMS: Modulating Intracortical Excitability

The paired-pulse paradigm applied to the motor cortex (Claus *et al.*, 1992; Valls-Sole *et al.*, 1992; Kujirai *et al.*, 1993) can be used to study corticocortical interactions and provides an array of potential clinical applications (see above). A few general findings from standard paired-pulse experiments of potential use in cognitive studies can be stated. Short interstimulus intervals (1–5 ms) can produce intracortical inhibition and slightly longer intervals (7–30 ms) produce facilitation. The mechanisms of these effects have been shown to be mediated by different cortical mechanisms—for example, lower intensity conditioning pulses are required for inhibition than for excitation; coil orientation, and thus direction of current flow, is critical for excitation but not inhibition, and the two phenomena can be independently affected by drugs and neurological disease (see Ziemann, 1999). The ability to potentially increase or decrease sensitivity of a cortical region over a short period of time has clear applications awaiting it in studies of priming, threshold detection, and cortical interactions. The work by Oliveri *et al.* on the role of the parietal lobe in attention employed this strategy for the first time.

Oliveri *et al.* (1999a) used TMS in a tactile stimulus detection task to demonstrate that the right, but not the left, parietal cortex is critical for detection not only of contralateral but also of ipsilateral stimuli. They found that bimanual discrimination is more readily disrupted than unimanual tasks, but only by right parietal TMS. Most importantly, they showed that the contribution of the right parietal cortex takes place around 40 ms after the tactile stimuli are applied, hence suggesting involvement of late cortical events. Fierro *et al.* (2000) extended these results showing that TMS can not only induce extinction to simultaneous visual stimulation of the two hemifields, but can also correct pseudoneglect. The neurophysiology of extinction might in fact be different from that of neglect, the latter being of greater clinical significance (Bisiach *et al.*, 1996; Kinsbourne, 1994; Vallar, 1998). Patients with neglect face tremendous difficulties in rehabilitation as they do not realize the extent of their own limitations. Understanding neglect better will hopefully aid in developing suitable methods for its treatment. Oliveri's and Fierro's results seem to support the widespread notion that the right hemisphere contains representations of both hemi-

spaces, while the left hemisphere is concerned with attending only to the contralateral hemispace. However, interhemispheric competition (possibly asymmetrical) of cortical or subcortical structures might be better suited to explain some of these effects. Only interhemispheric competition provides a plausible explanation for the puzzling effects, extensively studied in cats, by which visual hemineglect induced by a lesion of one posterior cortex can be paradoxically reversed by secondary damage to contralateral cortical and subcortical structures (Lomber and Payne, 1996). This notion has been experimentally tested with TMS in humans (see below, figure 23, Hilgetag, *et al.*, 2001). Using exactly the same logic, Oliveri *et al.* (1999b) have used TMS to test this notion in 28 patients with right ($n = 14$) or left ($n = 14$) brain lesions. Single-pulse TMS was delivered to frontal and parietal scalp sites of the unaffected hemisphere 40 ms after application of a unimanual or bimanual electric digit stimulus. In patients with right hemispheric damage, left frontal TMS significantly reduced the rate of contralateral extinctions compared with controls. Left parietal TMS did not significantly affect the number of extinctions compared with baseline. Left-brain-damaged patients did not show equivalent results. In them, TMS to the intact, right hemisphere did not alter the recognition of bimanual stimuli. TMS to the left frontal cortex in patients with right hemispheric lesions significantly reduced the rate of contralateral extinctions, even though, as mentioned above, the same type of stimulation did not affect task performance in normal subjects. These results suggest that extinctions produced by right-hemisphere damage may be dependent on a breakdown in the balance of hemispheric rivalry in directing spatial attention to the contralateral hemispace, so that the unaffected hemisphere generates an unopposed orienting response to the side of the lesion (Fig. 19). TMS to the left frontal cortex in patients with right hemisphere damage and contralesional extinction ameliorates their deficit. The mechanism of action of TMS in this setting could involve crossed frontoparietal inhibition. However, interactions at subcortical level cannot be excluded.

Oliveri *et al.* (2000) followed their study of right-brain-damaged patients with neglect, with an experiment in which paired-pulse TMS was used to induce selective intracortical inhibition or facilitation of the unaffected hemisphere depending on the interstimulus interval. The hypothesis was that cortical inhibition would result in an improvement and cortical facilitation in a worsening of contralesional extinction compared with baseline. Paired-pulse TMS with the interstimulus interval set at 1 or 10 ms was applied to the left parietal or frontal cortex at various intervals following bimanual electric digit stimulation. At an interstimulus interval of 1 ms, which leads to intracortical inhibition, paired-pulse TMS led to a greater improvement in extinction than that induced by single-pulse TMS (Oliveri *et al.*, 1999a) (Fig. 20). On the other hand, with paired-pulse TMS at 10 ms, which is believed to increase cortical facilitation, there

was a worsening of extinction compared with baseline and a complete reversing of the effects of single-pulse TMS (Fig. 20). These results shed further light on the mechanisms of tactile extinction. In addition, this study illustrates the potential of paired-pulse TMS to selectively modulate intracortical excitability and extend the results of single-pulse TMS.

F. Paired-Pulse TMS: Studying Corticocortical Connectivity

Paired-pulse TMS can consist in pairs of stimuli delivered at the same or different intensity through a single TMS coil, hence targeting a single brain area (see above). Alternatively, paired-pulse TMS can be set up as two stimuli delivered through two different coils targeting separate brain regions with a variable interstimulus interval. Such an application provides a unique opportunity to study corticocortical connectivity and the behavioral role of feedback and feed-forward connections between brain regions. Pascual-Leone and Walsh (2001) have provided the first illustration of such a methodology in the study of visual awareness.

The role of primary visual cortex (V1) in awareness is a matter of long-standing and ongoing debate. While some investigators argue that specialized modules of visual cortex are autonomous and can lead to visual awareness on their own (i.e. without V1 contribution; see Zeki and Bartels, 1999; Zeki, 2001), others have maintained that the presence of V1 is necessary for conscious perception (see Stoerig and Cowey, 1997). Indeed, the extent and nature of residual visual capabilities of striate cortex-lesioned patients are still debated today. Destruction of primary visual cortex leads to blindness (hemianopsia) in the visual field contralateral to the lesion. However, numerous reports have detailed some residual capacities (mostly motion detection) in the blind field of destriate patients. One such patient is G.Y., a well-studied subject whose left striate cortex was almost entirely destroyed at the age of 8. The sometimes unconscious (blind-sight; see Weiskrantz, 1997) ability of G.Y. to perceive motion is associated with the integrity of the specialized motion area (MT/V5) in both hemispheres (see Zeki and ffytche, 1998). Cowey and Walsh (2000) used the capacity of TMS to induce phosphenes to explore the role V1 plays in visual awareness. When regions corresponding to V1 are stimulated, phosphenes are static and retinotopically organized, whereas MT/V5 stimulation can result in moving phosphenes (Stewart *et al.*, 1999). In G.Y., stimulation of the occipital pole of the intact hemisphere resulted in the perception of static phosphenes, as should be expected in a normal brain. Moreover, stimulating a region corresponding to motion area MT/V5 induced moving phosphenes. When TMS was applied to MT/V5 of the damaged hemisphere, no phosphenes were elicited, despite previous PET data showing MT/V5 activation in response to motion stimuli presented in the blind field (Barbur *et al.*, 1993). The authors

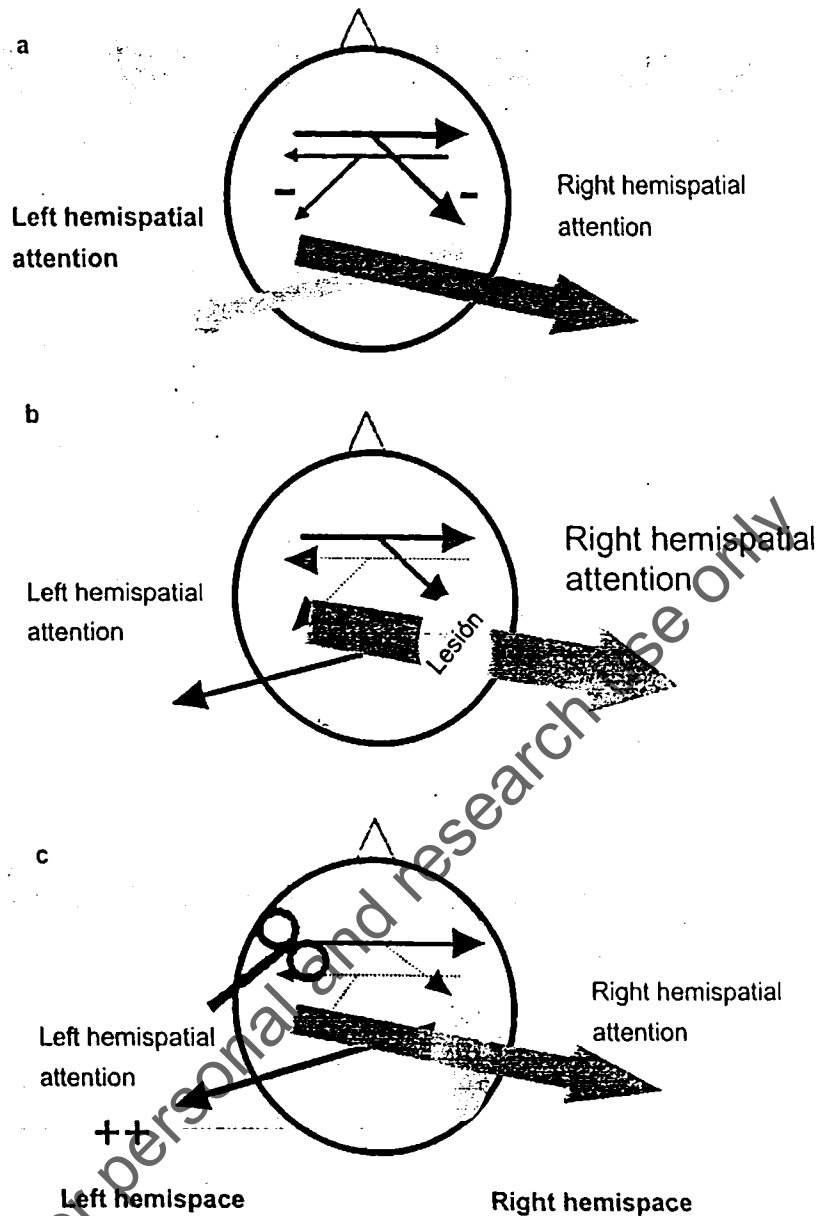


Figure 19 Proposed framework for left- and right-hemispheric contributions to the neural representation of egocentric space. In normal volunteers (A), the mutual inhibitory callosal connections between the two hemispheres are asymmetric with the dominant hemisphere exerting greater inhibition onto the nondominant hemisphere, hence producing a slight hyperorientation to the right side. Following a right-hemisphere stroke (B), the unbalanced effect of the left hemisphere results in excessive attention toward the right (ipsilesional) hemispace (dashed arrow). In right-brain-damaged patients, left frontal TMS interferes with the hypothesized left frontal–right parietal inhibition, thus disinhibiting the right parietal cortex and partially restoring left extinctions (black arrow). Modified from Oliveri *et al.* (1999a, 1999b), with permission.

applied high-intensity TMS at 36 positions over a 5×5 -cm grid centered over the expected position of V5 without eliciting one phosphene. These observations led to the conclusion that the absence of phosphenes “when TMS was similarly applied to extrastriate visual regions of a patient with hemianopia caused by destruction of V1 and parts of V2

suggests that TMS can only induce conscious visual perception when V1/V2 are intact.”

Using paired-pulse TMS delivered to separate brain areas, Pascual-Leone and Walsh (2001) have studied the conscious perception of phosphenes further (Fig. 21). Pascual-Leone and Walsh hypothesized that conscious perception of moving

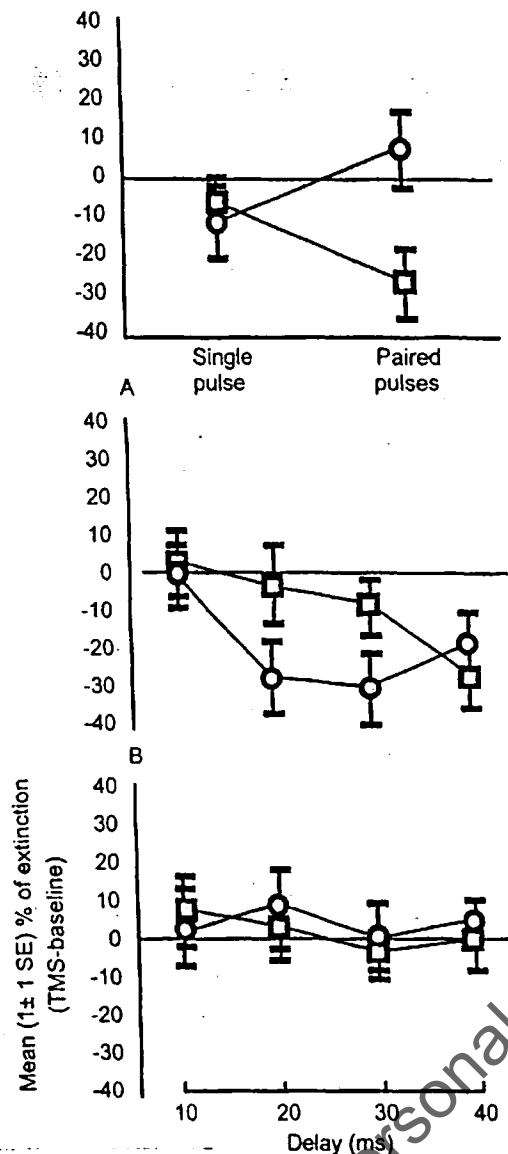


Figure 20 Mean percentage (\pm standard error) of contralesional extinction for single-pulse and paired-pulse TMS paradigms. Results express the difference between baseline and TMS conditions. Trials with paired-pulse TMS at 1 ms (filled squares) and 10 ms (open circles) show divergent results. See text for details. Modified from Oliveri *et al.* (2000), with permission.

phosphenes, induced by MT/V5 stimulation, may be dependent upon a feedback loop between MT/V5 and V1. A suprathreshold single-pulse TMS over MT/V5 was used to create a moving phosphene in normal subjects. This first pulse was followed by a second, subthreshold pulse over V1 between 0 and 90 ms later. If MT/V5-V1 feedback projections are necessary for the perception of phosphenes, the second pulse should disrupt perception of the attributes encoded by the extrastriate area. Indeed, when the V1 TMS pulse was applied 5 to 45 ms after the MT/V5 pulse, there was a marked decrease in the quality of phosphenes. In five

of the eight subjects studied, the double-pulse paradigm completely abolished the perception of phosphenes. These data suggest that magnetic stimulation of V1 disrupts the flow of information going from MT/V5 to primary visual cortex, which usually leads to conscious perception of a moving phosphene. In addition, this study illustrates the potential use of TMS to study the timing of corticocortical interactions and their causal role in behavior and cognition.

G. Online TMS and Offline TMS

The studies discussed above all applied TMS during task performance. TMS can also be used in what has been termed its distal or offline mode. Such offline use of rTMS in the study of cognition is based on studies of motor cortex in which it has been shown that a continuous train of stimulation can modulate cortical excitability beyond the duration of the rTMS train itself (Chen *et al.*, 1997; Berardelli *et al.*, 1998; Pascual-Leone *et al.*, 1998). Slow rTMS (1 Hz) applied to motor cortex can give rise to a lasting decrease in corticospinal excitability (Chen *et al.*, 1997; Maeda *et al.*, 2000) and it seems reasonable to assume a similar suppression of excitability when slow rTMS is applied to nonmotor cortical areas. This approach has recently been implemented in a number of cognitive studies, including visual perception (Kosslyn *et al.*, 1999), spatial attention (Hilgetag *et al.*, 2001), motor learning (Robertson *et al.*, 2001), working memory (Mottaghy *et al.*, 2001), and language (Shapiro *et al.*, 2001). It is hypothesized that application of slow rTMS to cortical areas other than motor creates similar decreases in cortical excitability which lead to measurable behavioral effects (Pascual-Leone *et al.*, 1999a). In this paradigm, performance on a given task is evaluated before (baseline) and after application of rTMS. This enables study designs in which the potential disruption of ongoing TMS on task performance is eliminated.

In the first application of this "offline" TMS strategy, Kosslyn *et al.* (1999) investigated the role of primary visual cortex in visual imagery using identical task conditions in a rTMS study and in a PET experiment. The PET results revealed activation of V1 during visual imagery and provided the target for the application of TMS. In the TMS experiment subjects received 1-Hz stimulation at 90% of motor threshold for 10 min to the area of activation in striate cortex in the subjects' PET scan. Following rTMS, subjects were required to visualize and compare the properties of memorized images of grating patterns or of real images of the same stimuli. The reaction times of subjects were significantly increased in both real perception and imagery conditions (Fig. 22), showing that area V1 was critical for visual imagery as well as real perception. The effect of TMS was greater for imagery than for real perception, which may reflect the fact that the imagery condition was harder than the perception condition.

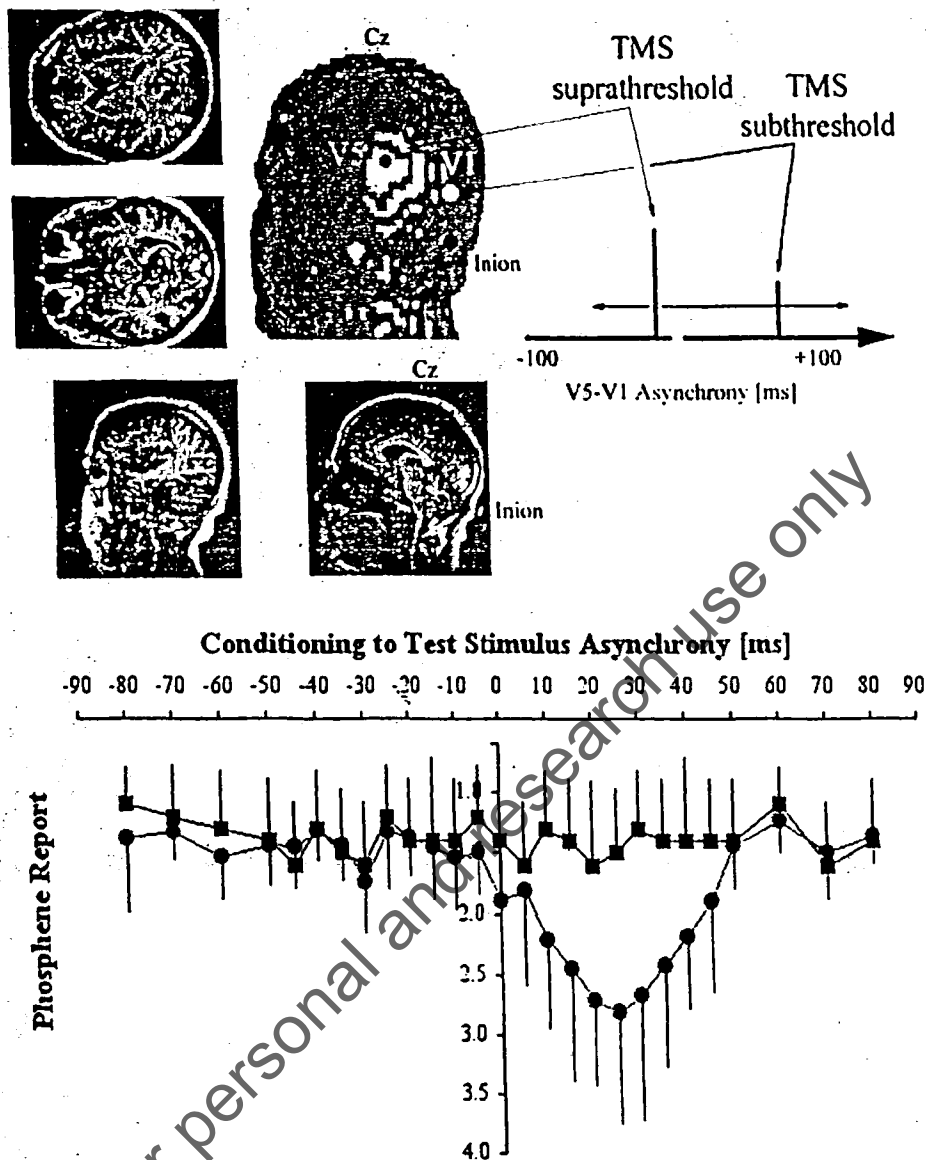


Figure 2 Reproduced from Pascual-Leone and Walsh (2001), with permission. Top: Schematic representation of the experimental design of a V5-V1 interaction study. The brain MR image from one of the study subjects displays a representative example of the site of stimulation for induction of stationary (V1) and moving phosphenes (MT+/V5). The location on the subject's scalp of the center of the intersection of the wings in the 8-shaped TMS coil is projected, perpendicular to the scalp surface, onto the subject's brain as reconstructed from an anatomical MRI. Bottom: Mean responses of all subjects ($n = 8$) to combined stimulation of V5 and V1. The V5-V1-TMS asynchrony is displayed on the x axis: negative values indicate that V1 received TMS prior to V5, and positive values indicate that V1 was stimulated after V5. The subjects made one of four judgments. The phosphene elicited by V5 TMS was (1) present and moving, (2) present but the subject was not confident to judge whether moving, (3) present but stationary, (4) not observed. TMS over V1 between 10 and 30 ms after TMS over V5 affected the perception of the phosphene.

H. Paradoxical Facilitations

Brain injury sometimes results in functional facilitations (see Kapur, 1996). The two main classes of facilitation have been termed "restorative," wherein a hitherto deficient function has returned (as in the Sprague effect), and "enhancing,"

in which some damage or loss of function results in the patient performing better than normal subjects at some task. Both classes of facilitation reveal much of interest about the dynamic interactions between different modalities or even components of sensory modalities. Nevertheless, as Kapur notes "such findings have often been ignored or undervalued

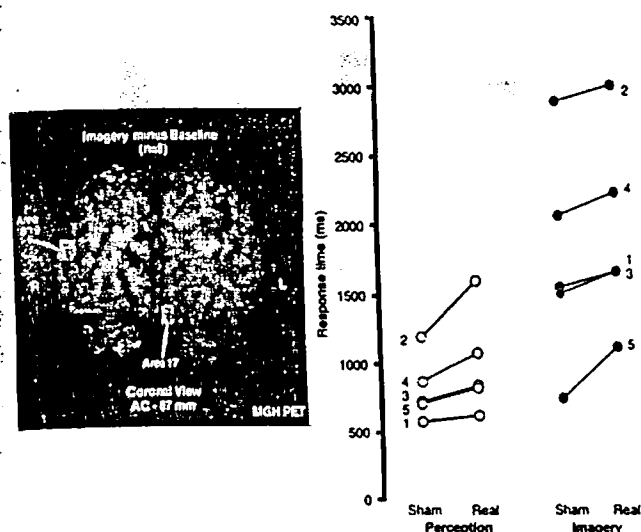


Figure 22 TMS and mental imagery. Results of delivering rTMS over occipital cortex before perception and imagery conditions. "Real" TMS occurred when the magnetic field was directed into area 17 and sham rTMS occurred when the field was diverted away from the head. TMS over visual cortex slowed response times in both perception and imagery conditions in all five subjects. Reproduced from Kosslyn *et al.* (1999), with permission.

in the brain-behavior research literature." Perhaps this is because paradoxical facilitations are less common and less alien than deficits and also more difficult to interpret. Recent neurocomputing work may be useful in imposing some direction and also constraints on the search for and interpretation of facilitatory effects of TMS (Hilgetag *et al.*, 1999; Young *et al.*, 1999, 2000). One simulation, for example, showed that the connectivity of a cortical area was a strong predictor of the effects of lesions on the rest of the network as well as how that area responded to a lesion elsewhere in the network. This may seem like a truism but the kind of connectivity analysis offered by these models is not really taken into account in classical lesion analysis (see also Robertson and Murre, 1999; Rossini and Pauri, 2000) and the modeling work has begun to make these predictions explicit and testable.

In the visual system Walsh *et al.* (1998) stimulated visual area V5 in an attempt to model the "motion-blind" patient L.M. (Zihl *et al.*, 1983) and indeed V5 stimulation did impair performance on visual search tasks that involved scanning complex motion displays. On displays in which motion was absent or irrelevant to task performance, subjects were faster with TMS than in control trials. This can be interpreted as evidence that the separate visual modalities may compete for resources and the disruption of the motion system may have liberated other visual areas from its influence. In this experiment the subjects received blocks of trials of a single type and therefore knew whether the upcoming stimulus array would contain movement or color or form as the important parameter. When the types of trials are interleaved such that

the subject does not have advance information the enhancing effects of TMS were not obtained. Thus it seems that a combination of priming (due to the advanced knowledge of the stimuli) and weakening of the V5 system (by TMS) was required to enhance performance on color and form tasks. Conceptually similar is the finding of Seyal *et al.* (1995), who observed improvements in tactile sensitivity as a result of stimulation of the somatosensory cortex ipsilateral to fingers being tested. The interpretation here is also based on disinhibition of the unstimulated hemisphere.

The facilitations reported by Walsh *et al.* were obtained with online TMS but similar effects have been reported using distal TMS. A clear example of interhemispheric rivalry revealed by offline rTMS has recently been reported by Hilgetag *et al.* (2001) in a study designed to address the notion of interhemispheric competition in guiding attention. They found ipsilateral enhancement of visual attention, compared to normal performance (Fig. 23), produced by rTMS of the parietal cortex at stimulation parameters known to reduce cortical excitability. Healthy, right-handed volunteers received rTMS (1 Hz, 10 min) over right or left parietal cortex (at P3, P4 EEG coordinate points, respectively). Subsequently, subjects' attention to ipsilateral visual targets improved significantly while contralateral attention diminished. Additionally, correct detection of bilateral stimuli decreased significantly, coupled with an increase in erroneous responses for ipsilateral unilateral targets. Application of the same rTMS paradigm to motor cortex as well as sham magnetic stimulation indicated that the effect was specific for stimulation of parietal cortex. These results underline the potential of focal brain dysfunction to produce behavioral improvement and provide experimental support for models of visuospatial attention based on the interhemispheric competition of cortical components in a large-scale attentional network.

V. TMS Limitations

A. Safety Considerations

The safety of single-pulse stimulation is well established but further precautions should be taken when using repetitive-pulse TMS. The magnetic field produced by stimulating coils can cause a loud noise and temporary elevations in auditory thresholds have been reported (Pascual-Leone *et al.*, 1993). 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

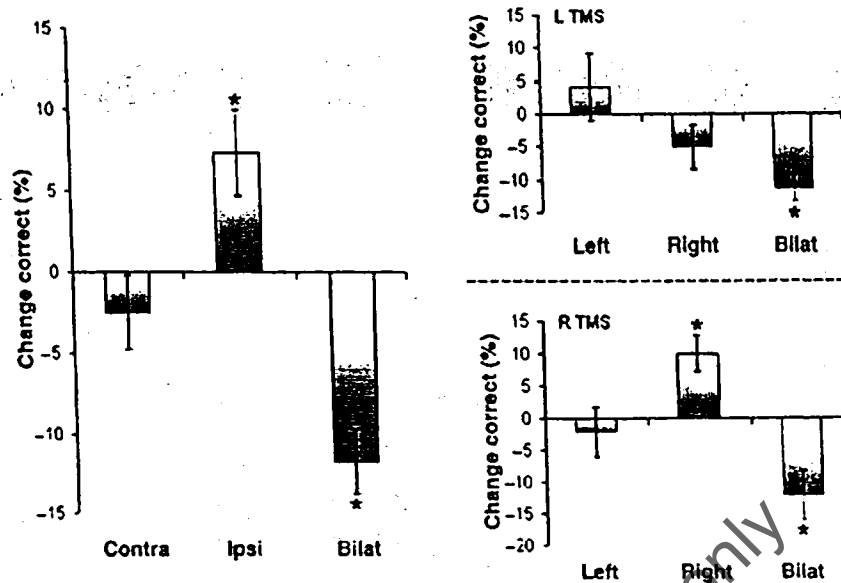


Figure 23 Modified from Hilgetag *et al.* (2001), with permission. Changes in correct stimulus detection after parietal rTMS. The diagrams are based on changes in the number of correctly detected stimuli (relative to the total number of presented stimuli) averaged for both stimulus sizes and all subjects. (a) The pooled data show a significant increase in performance ipsilateral to the parietal rTMS location (increase in relative percentage points 7.3%, SEM 2.6%) and a trend to decreased contralateral performance (reduction by 2.5%, SEM 2.3%). In addition, detection of bilateral stimuli decreased significantly (-11.7%, SEM 2.0%). These trends are also apparent after separating data for (b) left parietal TMS and (c) right parietal rTMS. Significant trends (as determined by Z tests, are marked by stars.

family history of epilepsy or other neurological condition should be precluded from taking part in an experiment which does not involve investigation of that condition. Pascual-Leone *et al.* (1993) 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. However, the paper is not exhaustive—it is based on only three sites of stimulation and expresses pulse intensity as a percentage of motor threshold. It has recently been argued that studies which apply rTMS to areas other than the motor cortex cannot simply lift stimulation parameters and criteria based on motor cortex excitability and assume they transfer to other conditions. There is no necessary relationship between motor cortex excitability and that of other cortical regions (Stewart *et al.*, 2001). It is also recommended that anyone wishing to use rTMS visit the TMS Website (<http://pni.unibe.ch/mail-list.htm>). The TMS community is constantly reviewing safety procedures and this Website is a starting point for access to sound information (although much of it is directed to a clinical audience). A more recent paper (Wassermann, 1998) summarizes the consensus that exists within the TMS 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 (Pascual-Leone, *et al.*, 1996; George *et al.*, 1995, 1996) 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 noted, however, that the improvements in mood as a result of rTMS follow several sessions of magnetic stimulation and the effects were cumulative (Pascual-Leone, *et al.*, 1996; George *et al.*, 1995, 1996). A simple precaution that may be taken is to prevent individual subjects from taking part in repeated experiments over a short period of time. The use of rTMS should follow a close reading of the reports of Pascual-Leone *et al.* (1993) and Wassermann (1998).

Niehaus *et al.* (1999) have approached this question using transcranial Doppler sonography (a noninvasive technique that allows blood flow, as velocities, to be recorded from intracranial arteries; see Bogdahn, 1998) to observe rapid changes in the hemodynamic response to TMS and to compare this with "real" sensory (in this case, visual) stimulation. As Fig. 24 shows, TMS produced changes in blood flow that occurred earlier and were larger in the hemisphere ipsilateral to stimulation over the occipital lobe. There was

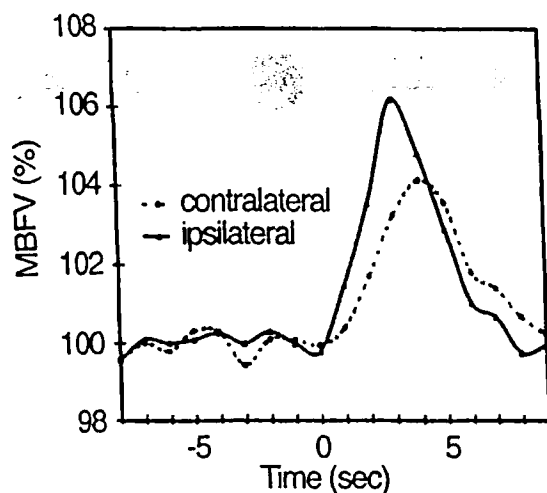


Figure 24 The cerebral hemodynamic response to TMS over the motor cortex in 10 subjects. Five trains of 10 Hz were given to each subject. Time-locked average MBFV changes in the middle cerebral artery ipsilateral and contralateral to the stimulation site is shown. Reproduced from Niehaus *et al.* (1999), with permission.

also a close correspondence between blood flow associated with trains of 5-Hz TMS and 5-Hz light flicker (Fig. 25), thus supporting the assumption that blood flow changes evoked by TMS are a reflection of neural activity rather than nonspecific effects on the vascular system. Importantly, there were no long-term changes associated with the rTMS.

B. Spatial Resolution

Several converging lines of evidence now show that there is good reason for confidence in the anatomical, but more

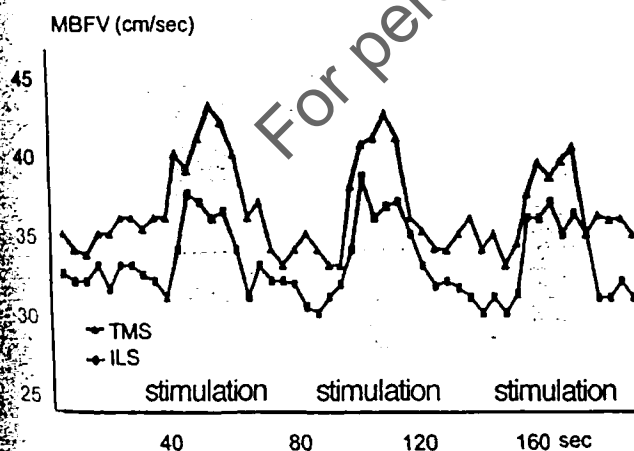


Figure 25 Changes in MBFV in the left posterior cerebral artery during rTMS over the left occipital cortex or visual stimulation with light flicker. Stimulation was performed with rTMS trains of 5 Hz and 20-s duration and intermittent visual stimulation (ILS) with the same frequency and stimulation duration.

importantly in the functional, specificity of TMS. One could simply appeal to the surface validity of TMS—Barker's first demonstration of motor cortex stimulation, for example, was itself strongly suggestive of relatively selective, suprathreshold stimulation of the hand area of the cortex. Perhaps there was some spread of current to arm, shoulder, and face regions of the motor cortex, but in the absence of movements from these parts of the body one must infer that the stimulation was *effectively* precise, i.e., stimulation of the other areas was subthreshold for producing a behavioral effect. There are many other examples of surface validity: phosphenes are more likely if the coil is placed over the visual cortex (Meyer *et al.*, 1991; Kastner *et al.*, 1998; Kammer, 1999; Marg, 1991; Stewart *et al.*, 1999), speech arrest is more likely if stimulation is applied over facial motor or frontal cortex (Pascual-Leone *et al.*, 1991; Epstein *et al.*, 1996b; Stewart *et al.*, 2001a), and neglect and extinction-like deficits are more likely if the coil targets the parietal lobe (Pascual-Leone *et al.*, 1994c; Ashbridge *et al.*, 1997; Fierro *et al.*, 2000). Mapping of motor cortex with EMGs also shows precise mapping of the fingers, hand, arm, face, trunk, and legs in a pattern that matches the gross organization of the motor homunculus (Singh *et al.*, 1991), sensitive both to coil location and to intensity (Brasil-Neto *et al.*, 1992a,b). There are also more direct measures of the specificity of TMS. Wassermann *et al.* (1996) mapped the cortical representation of a hand muscle with TMS and coregistered the inferred volumetric fields with anatomical MRIs from each subject, and these were in turn coregistered with PET images obtained while subjects moved the finger that had been mapped with TMS. In all subjects the estimated fields induced by TMS met the surface of the brain at the anterior lip of the central sulcus and extended along the precentral gyrus for a few millimeters anterior to the central sulcus. Compared with the PET activations the MRI locations were all within 5–22 mm—an impressive correspondence across three techniques. A similarly impressive level of correspondence has also been seen in other studies that have correlated TMS with fMRI (Terao *et al.*, 1998a,b) and with MEG (Morioka *et al.*, 1995a,b; Ruohonen *et al.*, 1996). There are reasons for caution in interpreting these data (see Wasserman *et al.*, 1996), for example, the hand area activated lies deep in the central sulcus, possibly too deep to be directly activated by TMS and therefore presumably activated transsynaptically. The evidence for transsynaptic activation comes from a comparison of the EMG latencies elicited by electrical or magnetic stimulation (Day *et al.*, 1987, 1989a; Amassian *et al.*, 1990). Magnetically evoked latencies are approximately 1–2 ms longer than electrically evoked ones and this can be explained on the basis of which neurons are most likely to be stimulated by each technique (Rothwell, 1997). TMS is more likely to stimulate neurons that run parallel to the cortical surface, whereas electrical stimulation can directly stimulate pyramidal output

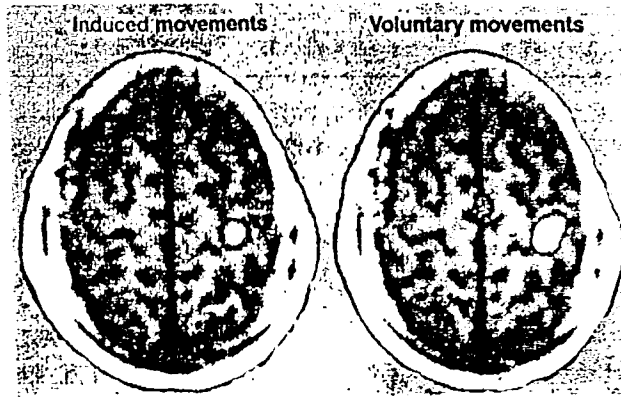


Figure 26 The spatial and functional specificity of TMS is evident in the correspondence between blood flow changes induced by TMS over the motor cortex to produce a finger movement and the activity produced by intentional movement which also produces SMA activity. Reproduced from Siebner *et al.* (1998), with permission.

neurons that run orthogonal to the cortical surface. Thus the 1- to 2-ms delay between electrical and magnetic cortical stimulation may be accounted for by the time taken for the stimulation to be transmitted from the interneurons to the pyramidal cells. Knowledge of which kinds of cells are stimulated based on temporal information can inform the interpretation of functional specificity.

Further evidence of the accuracy of TMS is seen in Fig. 26. Siebner and colleagues compared the changes in regional cerebral blood flow caused by 2-Hz rTMS over the motor cortex, sufficient to elicit an arm movement, with

blood flow changes due to the actual movement of the arm. The correspondence was striking. TMS-induced movements and voluntary movements both activated SM1 (area 4) ipsilateral to the site of stimulation. Voluntary movement also activated ipsilateral SMA (area 6) and the motor activity associated with the voluntary movement was more extensive than that elicited by rTMS. This could be because the voluntary arm movement was slightly greater than the TMS movement or because voluntary activity would involve more muscles than TMS activity. Whatever the difference, it is a clear example of the specificity of TMS and the physiological validity of TMS effects. Further evidence comes from studies of TMS effects measured by fMRI by George and Bohning and their colleagues (Fig. 27). These studies are important examples of the spatial specificity of TMS—they do not mean that the induced electric field is limited to the functional units stimulated, nor do they suggest that activation of neurons is limited to the areas seen in PET and fMRI; but they show unequivocally that the theoretical spread of the induced field is not the determinant of the area of effective stimulation and that the functional localization of TMS is, to a significant degree, under experimenter control.

Studies of EEG responses by Ilmoniemi and colleagues (1997) provide another demonstration of the relative primary and secondary specificity of TMS. As Fig. 28 shows, stimulation over the visual or motor cortex elicits EEG around the site of stimulation in the first few milliseconds after TMS. Within 20–30 ms this activity is mirrored by a secondary area of activity in the homotopic regions of

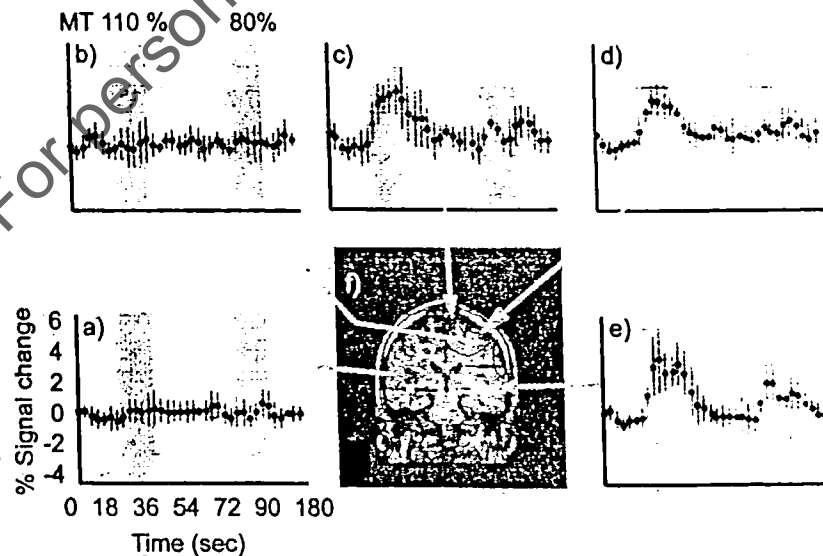


Figure 27 Time activity curves of a subject's brain during rest and with TMS over the thumb representation of the motor cortex. These data were obtained by interleaving BOLD fMRI and TMS. The TMS was given at 1 Hz for 8 s. The spatial and temporal resolutions of the measurements are approx 2 mm and 3 s. Reproduced from Bohning, *et al.* (1999), with permission.

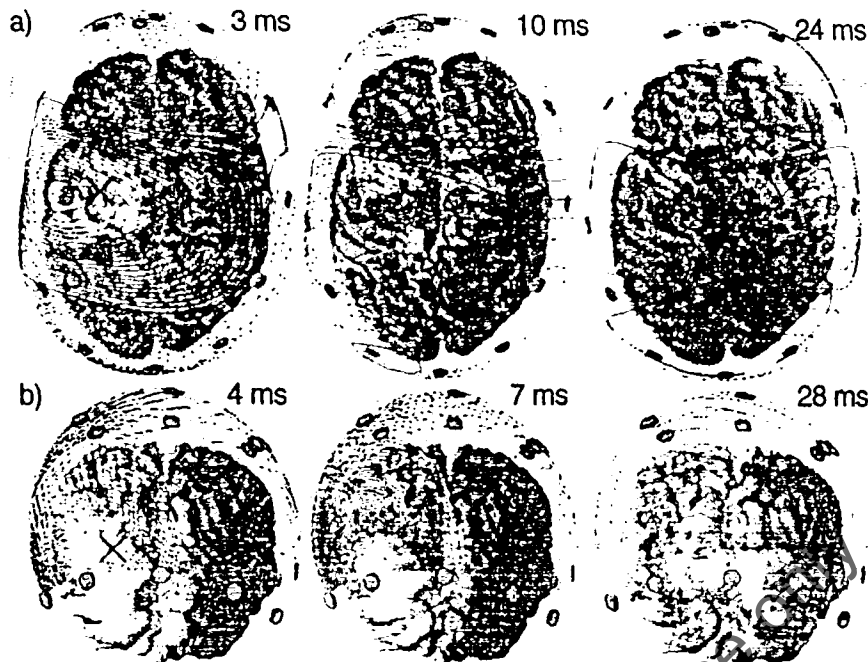


Figure 28 Duration of changes in neural activity induced by TMS. Four milliseconds after TMS over the occipital lobe most of the electrical activity recorded with high-resolution EEG is around the area directly under the TMS stimulation site (marked by the X). By 7 ms this has spread to the midline and by 28 ms there is clearly contralateral activation. Reproduced from Ilmoniemi *et al.* (1997), with permission.

the contralateral hemisphere. These delays in homotopic areas are a rich source of hypotheses regarding the timing of effects in interhemispheric interactions. The utility and specificity of this combination of techniques were further demonstrated by applying TMS to the motor cortex of a patient who had suffered a lesion to the right basal ganglia and had lost fine finger control in his left hand and some control of his left arm. When the intact hemisphere was stimulated EEG responses were seen in both the ipsilateral motor cortices. When the motor cortex ipsilateral to the affected basal ganglia was stimulated, some EEG was seen ipsilaterally but none was transmitted interhemispherically to the intact hemisphere.

Other evidence of the effective focality of TMS is shown in Fig. 29. Pascual-Leone and colleagues compared the correspondence between the sites stimulated in an experiment targeting the motor cortex and the inferior frontal gyrus. The position of the motor cortex across 20 subjects was remarkably consistent with respect to the precentral sulcus, but there was considerable variability in the location of the frontal site relative to the inferior frontal and central sulci.

The depth of penetration of TMS is another important question and as with the question of lateral specificity there is no easy answer, but again there are good reasons to think that the approximations available are meaningful and can be used to guide interpretation of results. Models of the electric field at different depths from the coil suggest that relatively

wide areas are stimulated close to the coil, decreasing in surface area as the field is measured at distances farther from the coil. The image offered by these models is of an egg-shaped cone with the apex, which marks the point of the smallest area of stimulation, farthest from the coil. For a standard figure-8 coil, one estimate is that stimulation 5 mm below the coil will cover an area of approximately 7×6 cm. This area decreases to 4×3 cm at 20 mm below the coil, i.e., in the region of the cortical surface (Fig. 30). Calculations of induced electric fields as a function of depth can also be used as a guide to specificity because stimulation at points where the fields overlap allows subtraction of the effects. If a coil at position A disrupts performance on a behavioral task, the effective site of stimulation could be said to be anywhere within, around, or connected to the neurons crossed by the field. If stimulation at neighboring sites B and C fails to disrupt the task, then the overlap in fields between A and B and between A and C can be said to be ineffective regions of the field and the most effective field is the shaded subregion of A. Thus the notion of the effective resolution of TMS can be refined; whereas a single-pulse of TMS cannot be said to have a small, volumetric resolution in the cortex, from a functional point of view it can be shown to have a small scalp resolution and an inferred or subtracted volumetric resolution when multiple sites are compared. A comparison might be made here with fMRI and, say, a cortical area such as visual area V5 (Watson *et al.*, 1993); it is clearly

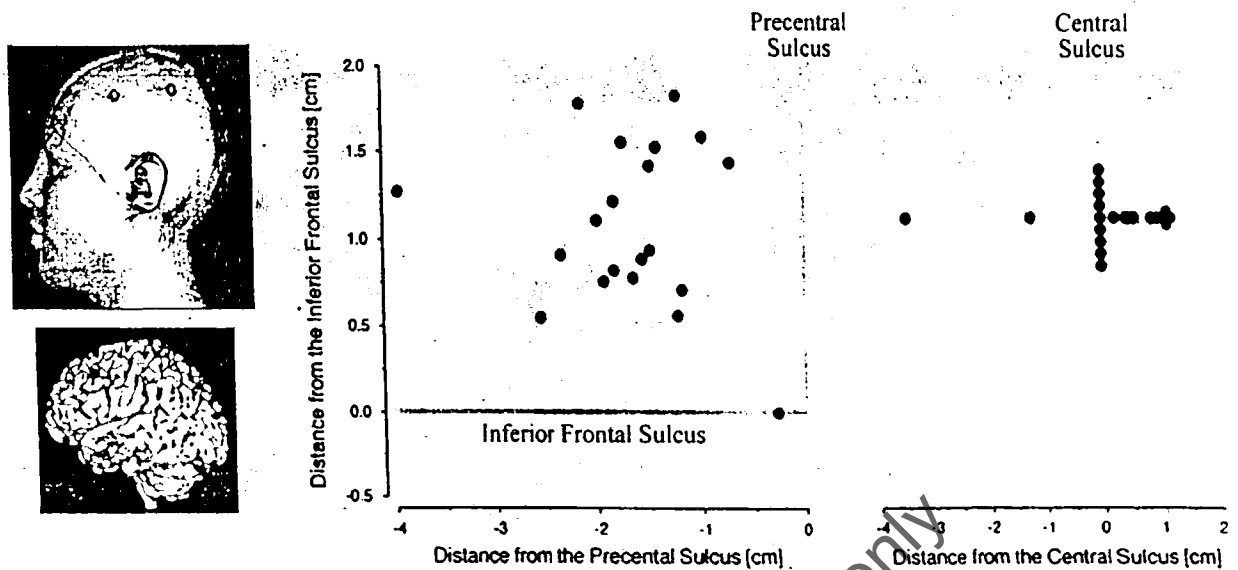


Figure 29 Identification of brain areas targeted by TMS—a comparison across subjects. Optimal sites for activation of abductor pollicis brevis muscle and from a scalp position 5 cm anterior to it and in the same parasagittal plane. Data from 20 subjects are presented. The position of the figure-8 coil on the scalp was marked with a vitamin A capsule and an MRI was obtained and reconstructed in three dimensions. The location of the capsule on the scalp was projected perpendicular to the skull surface onto the brain and the point of intersection with the projection line was marked. The scattergram displays these points (i.e., the brain area targeted by TMS) in relation to the central sulcus and in relation to the precentral and the inferior frontal sulcus. Reproduced from Pascual-Leone *et al.* (1999a), with permission.

not the case that moving visual stimuli activate V5 and V5 alone. Rather, the specificity of this area is, quite properly, inferred by subtracting the activations caused by stationary or colored stimuli or different kinds of visual motion.

C. Temporal Resolution

The cycle of a single pulse of TMS is approximately 1 ms (Fig. 2) and this determines the temporal resolution of the

application of TMS. The duration of the effect in the cortex is difficult to determine because the neurons stimulated by the field may take time to recover their normal functional state and normal interactions with other cells. Several TMS studies have applied single-pulse TMS at intervals of 10 ms and obtained effects that suggest TMS can distinguish processes within such a small time window—but the time window is probabilistic rather than fixed and depends on the interaction between the resources the stimulated area is

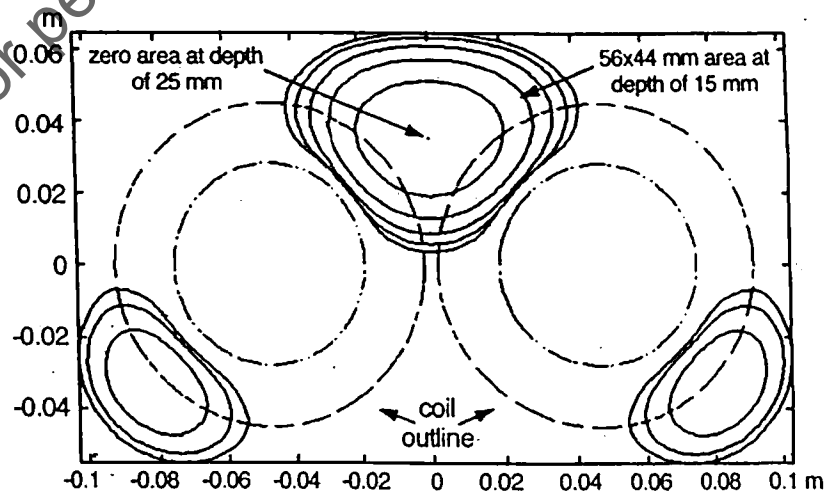


Figure 30 Estimated stimulation areas at depth intervals of 5 mm beginning at the cortical surface. Reproduced from Barker (1999), with permission.

giving to a task and the strength of disruption caused by the TMS pulse.

D. Local and Distant Effects

Other evidence strengthens the correlation between targeted and activated cortical regions. Paus and colleagues (1997, 1998; Paus and Wolforth, 1998; Paus, 1999) have carried out a number of studies in which TMS has been combined with analysis of PET activations using a method of frameless stereotaxy which aligns MRI landmarks and the center of the stimulating coil with an accuracy within 0.4–0.8 cm. The first critical finding of these experiments is that TMS has a major effect approximately under the center of a figure-8 coil, and secondary effects at sites that are known to be anatomically connected. In Chapter 25 Tomás Paus addresses these results and methods further. The finding of distant effects of TMS has obvious relevance in the interpretation of virtual lesion experiments that assume that behavioral consequences of rTMS are due to the disruption of the directly targeted brain region. In some instances, distant effects of rTMS may contribute or even account for behavioral consequences so that careful control experiments targeting different brain areas with TMS are critical.

Acknowledgments

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