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CHAPTER 12

Transcranial magnetic stimulation: a new tool for the study of higher cognitive functions in humans

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1. Introduction

Transcranial magnetic stimulation allows the non-invasive stimulation of the human cortex. Since the introduction in 1985 by Barker, Freeston, Jalinous et al. (1985a) and Barker, Jalinous and Freeston (1985b) of a compact coil stimulator, single pulse magnetic stimulation has become an invaluable tool for the evaluation of human motor system in health and disease (Mills, 1991; Rothwell, Thompson, Day et al., 1991; Murray, 1992). The recent development of stimulators capable of stimulating at frequencies up to 60 Hz appears to have greatly expanded the applicability of transcranial magnetic stimulation to the study of higher cognitive functions (Cadwell, 1991; Pascual-Leone, Gates and Dhuna, 1991c). Transcranial magnetic stimulation can provide unique information about the topographic and temporal organization of human cognitive processes and allows correlation of the objective behavioral effects of the stimulation with the subject's introspective perception.

Basically, magnetic stimulation represents a form of 'electrodeless electric stimulation' (Cadwell, 1989; Hallett, Cohen, Nilsson et al., 1989) that has the obvious advantage over direct electric cortical stimulation of not requiring a craniotomy. Therefore, in contrast to other techniques of cortical stimulation, transcranial magnetic stimulation allows the study of normal subjects rather than being restricted to the study of patients undergoing surgical procedures for medically intractable epilepsy or focal brain lesions. Transcranial magnetic stimulation is a virtually painless and safe technique (even if applied in high frequency trains) if appropriate safety guidelines are followed (Pascual-Leone, Houser, Reese et al., 1992b).

There are three basic effects of transcranial magnetic stimulation that can be used to study the physiological correlates of cognitive functions. (1) Single-pulse transcranial magnetic stimulation can be used to probe the excitability of neuronal networks. This allows comparison of the level of activation of different brain structures at different times during a task. Low intensity repetitive transcranial magnetic stimulation can be used to affect the level of excitability of such structures and thus manipulate the subject's responses or perceptions. In this fashion, transcranial magnetic stimulation can for example provide information about the organization of processes and neural structures in a reaction time task. (2) Single magnetic stimuli appropriately delivered in time and space can transiently block the function of neuronal networks. This allows examination of the effects of transcranial magnetic stimulation of different brain structures at different times on the subject's performance in a task. Repetitive transcranial magnetic stimulation may be necessary to interfere with complex cortical functions which

operate over extended periods of time. In this fashion, transcranial magnetic stimulation has been used to study the organization of visual and somatosensory perception, visual attention, voluntary motor acts, speech, language, and memory. (3) Finally, focal transcranial magnetic stimulation can be used to map the motor cortical outputs targeting contralateral muscles. Several maps can be obtained at different times in the same subject. This allows the study of cerebral plasticity associated with recovery of function after peripheral or central nervous system injuries, but also of the modulation of cortical outputs associated with and possibly underlying the acquisition of new motor skills.

The aim of this chapter is to give the reader an introduction to the history and physical principles of transcranial magnetic stimulation and an overview of our current level of knowledge on the potential uses of transcranial magnetic stimulation in cognitive neuroscience.

History of transcranial magnetic stimulation

Mutual induction, the principle on which magnetic stimulation is based was discovered by Faraday in 1831 (Faraday, 1839, 1965). The earliest reports on activation of the human central nervous system by magnetic fields date back to the 19th century (for a detail account on the history of magnetic stimulation of the nervous system, see Geddes (1991). Magnetic stimulation was first applied to the nervous system by d'Arsonval. In 1896 he described the induction of phosphenes, vertigo, and occasionally even syncope when subjects were exposed to an alternating magnetic field of 110 V, 30 A, and 42 Hz by placing their head inside the induction coil (d'Arsonval, 1896). In 1902, Beer also reported the induction of phosphenes by a magnetic field applied to the head (Beer, 1902). In the early 1900s, magnetophosphenes became an interesting area of research because alternating current was replacing direct current as the source of electrical energy and because of reports of powerhouse workers experiencing strange sensations in the vicinity of transformers carrying high-intensity alternating currents (Geddes, 1991). Thompson (1910), Dunlap (1911) and Magnuson and Stevens (1911) constructed slightly different magnetic coil stimulators and independently corroborated the reports of induction of visual sensations. However, that magnetophosphenes could be elicited from excitation of the retina, the optic nerve, or the occipital cortex, was not shown until years later (Barlow, Kohn and Walsh, 1947; Kolin, Brill and Broberg, 1959).

Kolin et al. (1959) were the first to demonstrate conclusively on a frog sciatic-nerve, gastrocnemius-muscle preparation that a magnetic field could stimulate a nerve. Bickford and Fremming (1965) were able to induce skeletal muscle twitches not only in animals but also in intact human subjects using a pulsed magnetic field. In the 1980s, Barker et al. (1985b) and Polson, Barker and Freeston (1982) developed the first compact magnetic coil stimulator at the University of Sheffield. Transcranial motor cortical stimulation was first performed in Merton's laboratory at the National Hospital in London that same year (Barker et al., 1985a). Since then, several companies have developed similar devices that are commercially available (for example Cadwell Inc., Novametrix, Magstim Co., Dantec, and Digitimer) and there is a growing number of laboratories that employ magnetic stimulation for the study of the central and peripheral nervous system.

The originally, commercially available 'single-pulse' magnetic stimulators were limited to stimulation rates of 0.3–0.5 Hz. At higher stimulation intensities, the capacitors would not charge up completely and the coil would overheat. More recently, stimulators have been developed that allow stimulation rates of up to 60 Hz but are based on the same principles and have the same attributes as the 'single-pulse' magnetic stimulators (Cadwell, 1991). The first such 'high frequency, repetitive' magnetic stimulator was developed by Cadwell Inc. In the meantime, Cadwell's 'High Speed Magnetic Stimulator' and Dantec's 'MagPro' are commercially available, and several laboratories have designed and are using similar devices (for example Dr. D. Claus et al. at the University of Erlangen-Nüremberg, Germany and Dr. J. Sgro et al. at the Medical College of Virginia, Richmond, VA, USA).

Technical principles of transcranial magnetic stimulation

The basic design of magnetic stimulators is quite simple (Fig. 1A). Storage capacitors are charged to a voltage determined by the stimulus strength required, and can then be discharged into a stimulating coil via solid state switches. There is no electrical or mechanical contact between the stimulator and the subject. The basic principle of magnetic stimulation is implicit in Faraday's law. A time-varying magnetic field can induce a voltage in a nearby conductor whereby the induced current will be proportional to the rate of change of the magnetic field. The magnetic field will be proportional to the current in the stimulating coil. Therefore, the current induced in the tissue (secondary current) will be proportional to the rate of change (i.e. first time derivative) of the current in the stimulating coil (primary current). The voltage of the primary current and the geometry of the stimulation coil will determine the strength and shape of the generated magnetic field and thus of the density and focality of the secondary current induced in the tissue. Thus, magnetic stimulation represents a form of 'electrodeless' stimulation in which the generated magnetic field bridges the gap between primary and secondary currents (Fig. 1B).

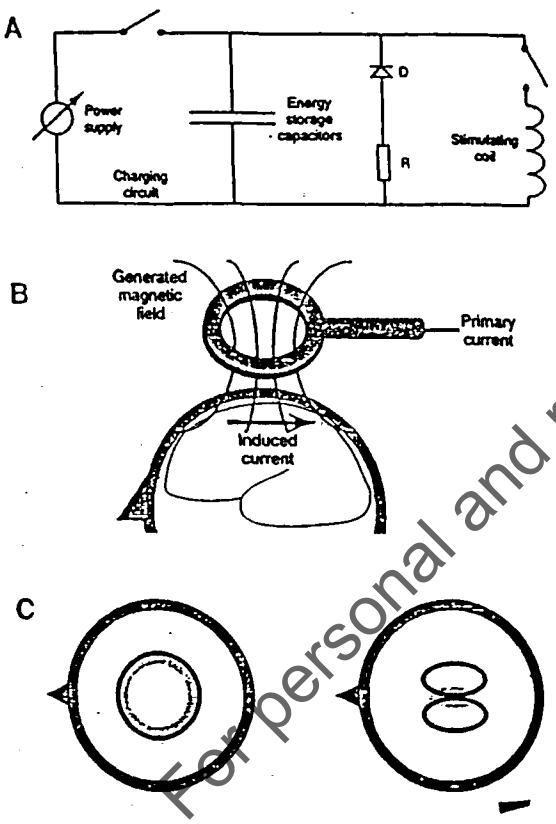

Fig. 1. (A) Simplified circuit diagram of a magnetic stimulator. (B) Schematic representation of the relationship between direction of current flow in the stimulation coil, generated magnetic field, and direction of flow of the secondarily induced current in the tissue. The focality of the stimulation depends largely on the size and geometry of the stimulation coil. (C) Schematic representation of the distribution of the maxima of the electric field produced at cortical level during magnetic stimulation using a circular coil and an 8-shaped coil held over the vertex and flat on the scalp. The thick line represents the coil windings, the gray dotted area represent the maxima of the induced electric field (for accurate model and detailed calculation of the electric field see Roth et al., 1991c; Saypol et al., 1991).

In the following paragraphs, we provide a brief introduction to the physical laws governing magnetic stimulation; for a more detailed discussion, the reader is referred to several recent authoritative reviews (Cadwell, 1989; Tofts, 1990; Barker, 1991; Jalinous, 1991; Roth, Cohen and Hallett, 1991a; Roth, Saypol, Hallett et al., 1991c).

A current pulse through the stimulation coil produces an electric field by Faraday induction. The electric field, E, is the negative of the time derivative, $\partial/\partial t$, of the vector potential, A.

$$E = -\frac{\partial A}{\partial t} \tag{1}$$

The vector potential A is proportional to the current in the coil and its spatial distribution is given by an integral over the path of the coil which can be solved numerically (Cohen, Roth, Nilsson et al., 1990).

During magnetic stimulation, the presence of the body influences the electric field E by virtue of the accumulation of charge on the tissue–air boundary. This influence can be expressed as the gradient (∇) of a scalar potential F (Roth et al., 1991a) so that

$$E = -\frac{\partial A}{\partial t} - \nabla F \tag{2}$$

The calculation of the scalar potential F is complicated because the charge distribution that arises on the tissue–air boundary is not known and must be solved by a differential equation. The scalar potential F obeys Laplace's equation in a homogeneous, isotropic volume conductor and thus

$$\nabla^2 F = 0 \tag{3}$$

On the tissue–air surface, $E\Sigma n$ is zero, where n is a unit vector perpendicular to the surface and the 'Σ' indicates the dot product between the two vectors. Therefore, according to eq. (2), the boundary condition for F is

$$\frac{\partial F}{\partial n} = -n\Sigma\frac{\partial A}{\partial t} \tag{4}$$

where $\partial/\partial n$ indicates the derivative of F in the direction of n. There are many techniques for solving Laplace's equation given a boundary condition on the conductor surface; for review see Roth et al. (1991c).

To a first approximation the head and the brain can be represented as a homogeneous sphere. The electric field induced in a spherical volume conductor has been calculated for several coil shapes and orientations (Cohen et al., 1990; Eaton, 1990). Figure 1C shows highly simplified plots of the maximal magnitude of the electric field induced in a spherical conductor by a circular and an 8-shaped coil. Using analogies to biomagnetism (Cohen and Cuffin, 1991; Yunokuchi and Cohen, 1991), it seems reasonable to propose that there is no radial component to the electric field in a spherical conductor. This proposal is consistent with the numerical calculations by Roth et al. (1991c), and has been proven analytically by Saypol, Roth, Cohen et al. (1991). It follows that if the head is represented by three concentric spherical shells (scalp, skull, cortex), then the electric field is independent of the conductivity of each layer. In particular, the presence of the high resistance skull does not affect the electric field.

However, the head and the brain are irregularly shaped, inhomogeneous volume conductors and therefore the numerical technique used to calculate the electric field must be extended. At present, the effect of inhomogeneities is unknown. To account fully for an irregular, inhomogeneous tissue would require an elaborate computation, perhaps using a finite-element program, and a knowledge of the conductivity distribution throughout the cortex. It seems clear however, that tissue inhomogenities are biologically relevant so that the brain structures stimulated by transcranial magnetic stimulation cannot be directly inferred from the available models of the induced electric fields. For example, Maccabee, Amassian, Eberle et al. (1993) have elegantly shown that neural structures are preferentially stimulated at bends in fiber bundles because of the drastically lowered activation threshold.

Neural elements activated by transcranial magnetic stimulation

Currents induced in the brain by transcranial magnetic stimulation flow parallel to the plane of the stimulation coil, i.e. approximately parallel to the brain's cortical surface when the stimulation coil is held tangentially to the scalp (Roth et al., 1991c; Saypol et al., 1991). Therefore, it seems reasonable to hypothesize that magnetic stimulation, in contrast to electrical cortical stimulation, will preferentially activate neural elements oriented horizontally, i.e. parallel to the cortical surface (Day, Thompson, Dick et al., 1987; Day, Dressler, Maartens De Noordhout et al., 1989a). Most of the intracortical horizontally oriented neural elements are interneurons. Preferential activation of such interneurons supports the hypothesis that over the motor cortex magnetic stimulation is more likely to activate pyramidal cells transynaptically thus producing indirect (I) waves (Amassian, Stewart, Quirk et al., 1987; Amassian, Cracco, Eberle et al., 1989a; Amassian, Cracco, Maccabee et al., 1990a; Day et al., 1987, 1989a). However, this fact seems to be highly dependent on stimulation intensity and coil orientation (Amassian, Quirk and Stewart, 1990b) and with high stimulation intensities, direct activation of pyramidal cells, as is found with electrical stimulation, is likely (Berardelli, Inghilleri, Cruccu et al., 1990; Inghilleri, Berardelli, Cruccu et al., 1990). Furthermore, this hypothesis of preferential activation of interneurons by

magnetic stimulation has been challenged by Edgley, Eyre, Lemon et al. (1990) who, based on stimulation studies in monkeys, have suggested that the differences between transcranial magnetic and electrical stimulation of the brain are not due to activation of different neural structures but rather the consequence of the more superficial site of action of the former.

In any case, regardless of whether neurons are activated transynaptically or at their initial segments, the effects of transcranial magnetic stimulation is highly dependent on cortical excitability. Therefore, transcranial magnetic stimulation represents an ideal tool for the study of the temporary level of activation of a cortical network during the performance of a task. This fact has motivated the study of the physiological correlates of several cognitive functions that are discussed below.

Spatial resolution of transcranial magnetic stimulation

Focality of the stimulation is an important technical requirement for the application of transcranial magnetic stimulation to the study of cognitive functions because of the need for precise spatial resolution. Focal transcranial magnetic stimulation has become possible with the development of stimulation coils of different geometries (Cohen et al., 1990; Maccabee, Eberle, Amassian et al., 1990; Cohen and Cuffin, 1991; Yunokuchi and Cohen, 1991). Cohen, Sato, Rose et al. (1989) and Levy, Amassian, Schimd et al. (1991) have shown that the results of non-invasive cortical motor mapping with transcranial magnetic stimulation using an 8-shaped coil correlate well with those obtained with direct cortical electric stimulation. Wassermann, Wang, Toro et al. (1992b) have shown that the cortical output maps obtained with transcranial magnetic stimulation indeed represent the results of stimulation of the anterior bank of the central sulcus by projecting the results of the magnetic stimulation maps onto the subject's brain magnetic resonance images. Successive stimulation of different scalp positions 1–2 cm apart with the 8-shaped coil lying tangentially to the scalp and centered over the stimulation position allows differentiation of proximal and distal arm muscles (Brasil-Neto, McShane, Fuhr et al., 1992c; Wassermann, McShane, Hallett et al., 1992a).

Recently, several studies have documented the effects of coil orientation and shape of the induced current pulse on the amplitudes of motor potentials evoked by transcranial magnetic stimulation (Boniface, Mills and Schubert, 1990; Brasil-Neto, Cohen, Panizza et al., 1992a). The optimal direction of current induced in the brain for activation of contralateral muscles seems to be approximately perpendicular to the central sulcus, flowing diagonally from back to front. The use of different orientations of a coil that delivers nearly monopolar current pulses allows differentiation of the areas of motor cortical output targeting very closely represented muscles, such as different hand muscles (Pascual-Leone, Cohen, Brasil-Neto et al., 1993a). This technique further improves the spatial resolution of non-invasive cortical mapping and may express differences in orientation of spatially overlapping but functionally distinct neuronal networks (Pascual-Leone, Cohen, Brasil-Neto et al., 1993b).

Characteristics of the different magnetic stimulators

There are two basic kinds of devices for magnetic stimulation, those that allow 'single pulse' stimulation, i.e. stimulation frequencies of maximally 0.5 Hz, and those that allow 'high frequency' stimulation, i.e. up to 60 Hz. As mentioned above, the most widely used single pulse magnetic stimulators are commercially available from Cadwell Inc., Magstim Corp., Dantec, and Digitimer. High frequency magnetic stimulators are commercially available from Cadwell Inc. and Dantec. The multiple pulse capability of these high frequency stimulators is implemented by minimizing coil resistance, using resonant designs, using larger, faster charging storage capacitors, increasing the number of capacitor banks, or providing a higher power supply (Cadwell, 1991). Repetitive discharges at high frequency lead to overheating of the wire windings of the stimulation coil which would limit the duration of the stimuli trains and repetition rates applicable. To prevent this limitation, Cadwell's high

speed magnetic stimulator can be equipped with specially designed stimulation coils which allow continuous water cooling.

Another available alternative to allow multiple pulse capabilities is the 'MagStim Bistim Module'. This device allows serial connection of two MagStim single pulse magnetic stimulators so that pairs of magnetic stimuli can be delivered with variable interstimulus intervals down to milliseconds. In addition, the stimulation intensity of each pulse can be varied separately.

For all commercially available magnetic stimulators the current flowing through the stimulation coil reaches peaks of approximately 5000 A and generates a magnetic field of about 1–2 T at maximum (Burgess, 1991). However, the pulses of current delivered by the different stimulators are quite variable not only in the pulse duration but also in the number of phases. For example, the Dantec stimulator delivers a nearly monophasic pulse of 600 μs duration, the Cadwell MES-10 delivers an overdamped, polyphasic pulse, and the Cadwell High Speed Magnetic Stimulator delivers a biphasic, cosine pulse of 200 μs duration. The Dantec MagPro allows selection of the desired waveform, either a 200 μs biphasic pulse or a 600 μs monophasic pulse. The waveshape delivered by the stimulator is a relevant variable in the physiological effects of the stimulation and also determines the direction of current induced in the brain (Brasil-Neto et al., 1992a; Cohen et al., 1990).

Safety of transcranial magnetic stimulation

The safety of transcranial magnetic stimulation is supported by the long-standing experience with cortical electric stimulation in animals and humans and by a series of safety studies using transcranial magnetic stimulation in humans. The experience accumulated since 1985 suggests that single pulse transcranial magnetic stimulation lacks significant side-effects in normal subjects (Bridgers and Delaney, 1989; Claus, 1989; Levy, Oro, Tucker et al., 1989; Dressler, Voth, Feldmann et al., 1990; Bridgers, 1991; Pascual-Leone, Cohen, Shotland et al., 1992d; Pascual-Leone, Houser, Grafman et al., 1992a; Hamano, Kaji, Fukuyama et al., 1993), although it can induce seizures in predisposed individuals (Hömberg and Netz, 1989; Hufnagel, Elger, Durwen et al., 1990a; Kandler, 1990; Tassinari, Michelucci, Forti et al., 1990; Fauth, Meyer, Prosiegel et al., 1992). However, rapid-rate, repetitive transcranial stimulation has the potential to cause skin burns in the presence of electrodes, headache, temporary threshold shifts and tinnitus, and even inducing seizures in patients with epilepsy and in normal subjects (Pascual-Leone, Dhuna, Roth et al., 1990; Dhuna, Gates and Pascual-Leone, 1991; Roth, Pascual-Leone, Cohen et al., 1991b; Pascual-Leone Gates and Dhuna, 1991b; Pascual-Leone et al., 1991c, 1992a,b) . Therefore, caution is warranted in the use of rapid-rate transcranial stimulation and specific safety guidelines have to be followed to avoid the occurrence of such complications (Pascual-Leone et al., 1992b).

Exposure to transcranial magnetic stimulation, regardless of stimulation frequency, does not result in any lasting effects on neurological status, physical exam, or cognitive performance as evaluated by standard neuropsychological tests (Bridgers and Delaney, 1989; Bridgers, 1991; Dhuna et al., 1991; Ferbert, Mussmann, Menne et al., 1991; Pascual-Leone et al., 1992b). Saltuari, Marosi, Kofler et al. (1990) found a slowing in reaction time following transcranial magnetic stimulation. However, these findings have not been corroborated by others (Pascual-Leone et al., 1992a,b).

The discharge of the magnetic stimulation coil generates a very loud acoustic artifact that has the potential of affecting hearing both in the experimenter and in the subject (Counter, Borg, Lofquist et al., 1990; Counter, Borg and Lofquist, 1991). No hearing loss has been found in subjects exposed to multiple sessions of single pulse transcranial magnetic stimulation (Pascual-Leone, Valls-Solé, Brasil-Neto et al., 1992c). However, frequency of stimulation may be a very significant variable because of the relative timing of the protective middle ear acoustic reflex and the transient period of increased susceptibility to noise-induced hearing loss which follows exposure to high intensity noise (Pascual-Leone et al., 1992a,b). Temporary threshold shifts on the audiogram and tinnitus were found in several subjects exposed to rapid-rate tran-

scranial magnetic stimulation at frequencies up to 25 Hz (Pascual-Leone et al., 1992b). Therefore, the use of protective earplugs, which attenuate the acoustic artifact to safe levels is warranted under these conditions (Counter et al., 1990; Pascual-Leone et al., 1992b).

Following uncomplicated transcranial magnetic stimulation, no changes in hypothalamic hormone levels (prolactin, ACTH, TSH, LH and FSH) have been documented in studies applying single-pulse (Bridgers and Delaney, 1989; Levy et al., 1989) and repetitive transcranial magnetic stimulation (Hufnagel, Elger, Klingmüller et al., 1990b; Pascual-Leone et al., 1992b). This suggests that transcranial magnetic stimulation does not affect deep cerebral, limbic structures; a finding predicted by the results of modeling of the electric fields induced in the brain (Roth et al., 1991a; Saypol et al., 1991).

Transcranial magnetic stimulation does not seem to have any lasting effects on the electroencephalographic (EEG) activity in normal subjects. This has been documented for single pulse magnetic stimulation (Bridgers and Delaney, 1989; Levy et al., 1989) and for rapid-rate stimulation at frequencies up to 25 Hz (Pascual-Leone et al., 1992b). However, in patients with epilepsy, transcranial magnetic stimulation may have a variety of effects on the epileptic focus (Hufnagel and Elger, 1991) including an increase (Hufnagel et al., 1990a) or decrease in spike frequency (Steinhoff, Stodieck, Schreiner et al., 1991). These effects of magnetic stimulation are likely to depend on the stimulation frequency (Pascual-Leone and Dhuna, 1992). It is important to note that in the presence of EEG electrodes, rapid-rate transcranial magnetic stimulation can lead to skin burns because of the induction of eddy current and overheated electrodes (Pascual-Leone et al., 1990; Roth et al., 1991b). Special precautions need to be taken when recording EEG during transcranial magnetic stimulation which are summarized by Roth et al. (1991b).

The induction of seizures is very rare with single-pulse transcranial magnetic stimulation, even in epileptic and predisposed patients (Claus, 1989; Hömberg and Netz, 1989; Hufnagel et al., 1990a; Kandler, 1990; Tassinari et al., 1990; Fauth et al., 1992). However, this danger is much more prominent when using trains of transcranial magnetic stimulation. Hufnagel et al. (1990a, 1991) reported activation of the seizure focus and induction of partial complex seizures in patients with focal epilepsy. Dhuna et al. (1991) reported induction of a focal, secondarily generalized seizure in an epileptic patient exposed to high intensity stimulation at 25 Hz. Benecke et al. (personal communication) have also observed three epileptic patients in whom repetitive transcranial stimulation over the vertex resulted in induction of seizures. In addition, high intensity rapid-rate transcranial magnetic stimulation can induce after-discharges and even seizures in a normal subjects without significant risk factors for epilepsy (Pascual-Leone et al., 1992a,b). It is clear that rapid-rate, repetitive transcranial magnetic stimulation can lead to seizures and caution is warranted.

Rapid-rate transcranial magnetic stimulation can lead to a spread of cortical excitation over the course of a stimulation train even though the coil remains centered over a single scalp position (Pascual-Leone et al., 1992b). This induction of spread of excitation depends on the train duration, the stimulation frequency and intensity (Pascual-Leone, Valls-Solé, Wassermann et al., 1994b). Prolonged trains of appropriate frequency may result in such widespread horizontal excitation that re-entering, self-regenerating activity could develop and lead to a focal seizure (even in subjects without predisposing factors). In addition, the induction of spread of excitation raises the concern that magnetic stimulation might induce 'kindling'. Kindling refers to the process whereby repeated administration of a subconvulsive stimulus results in progressive intensification of the induced electric activity (Goddard, McIntyre and Leech, 1969). An animal is 'kindled' when the initially subconvulsive stimulus induces seizures that eventually may occur spontaneously, without preceding stimulation. The basic mechanisms thought to underlie kindling are similar to those discussed in relation to spread of cortical excitability induced by repetitive transcranial magnetic stimulation (Pascual-Leone et al., 1992b, 1994b). Even though the relevance of kindling in human epilepsy remains controversial

(Goldensohn, 1984; Morrell, 1991), it is a potential risk of transcranial magnetic stimulation. No danger of kindling should exist if rapid-rate transcranial magnetic stimulation is used at intensities and frequencies below those required to produce a spread of cortical excitation (Table 1). Nevertheless, these guidelines have to be periodically reviewed and studies specifically addressing this issue in animal models are needed.

The lack of structural damage to the brain following repetitive magnetic stimulation has been documented in temporal lobectomy specimens from two epileptic patients who underwent high frequency magnetic stimulation before surgery (Gates, Dhuna and Pascual-Leone, 1992). Sgro, Stanton, Emerson et al. (1991) found no anatomo-pathological changes in the brains of 11 rats exposed to at least 10 000 stimuli at 8 Hz and a peak field strength of 3.4 T. Mano, Finakawa, Nalamuro et al. (1989) and Hersh, Green, Weissman et al. (1990) have also reported no cerebral pathological changes induced by transcranial magnetic stimulation. However, Matsumiya, Yamamoto, Yarita et al. (1992) reported that ≥100 transcranial magnetic stimuli of high intensity (2.8 T) induced microvacuolar changes in the neuropil portion of cortical layers 2–6 in half of the rats studied. The reasons for the apparent discrepancy between these findings are unclear. The pathological changes reported by Matsumiya et al. (1992) could be due to differences in the techniques used to anesthetize the animals or study their brains, or might represent a transient and reversible phenomenon. In any case, the importance of this issue warrants attention and more studies on the potential risk of cortical damage induced by magnetic stimulation are needed. In this context, the choice of the animal model becomes an essential consideration. The efficiency of magnetic stimulation is drastically altered by brain size and the results of some of the available safety studies conducted with small animals using large stimulation coils may not at all be valid for human studies (Weissman, Epstein and Davey, 1992).

Determination of hemispheric speech dominance using rapid-rate transcranial magnetic stimulation

The intracarotid sodium amytal or Wada test is performed prior to surgical intervention for epilepsy to

TABLE 1

Guidelines for selection of trains of rapid-rate transcranial magnetic stimulation (roots) that do not lead to spread of cortical excitation and are therefore considered safe (see text for details)

rTMS frequency (Hz)	rSMS intensity (% of threshold)												
	100	110	120	130	140	150	160	170*	180*	190*	200#	210#	220#
A. Time (s) until spread of excitation during roots													
1	>50	>50	>50	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	1.6	1	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08
B. Number of magnetic pulses (n) until spread of excitation during rTMS													
1	>50	>50	>50	>50	>50	>50	>50	27	11	11	8	7	16
5	>50	>50	>50	>50	38	26	18	13	12	8	7	8	6
10	>50	>50	42	29	13	8	9	8	5	6	4	3	3
20	41	32	20	11	7	5	5	3	4	5	4	2	2
25	32	21	10	6	5	6	5	3	2	3	3	2	2

Data reflect the lowest values of time or number of pulses that result in spread. Data are based on studies on >30 subjects, >15 subjects (*), or 5–10 subjects (#).

determine the language dominant hemisphere (Wada and Rasmussen, 1960; Serafetinides, Hoare and Driver, 1965; Engel, 1987). However, the short lasting effect of amytal and the possibility of inter-hemispheric cross-over of the drug, limit the time for testing and may interfere with the results. In addition, the procedure has an estimated morbidity of 1–3% (Engel, 1987). Therefore a non-invasive, safer technique for determination of language dominance would be helpful. Several studies suggest that rapid-rate transcranial magnetic stimulation might be developed into such a technique.

In 1991, Pascual-Leone et al. (1991c) published the first report on the use of rapid-rate repetitive transcranial magnetic stimulation for the non-invasive determination of the language dominant hemisphere. Six adult epileptic patients underwent rapid transcranial magnetic stimulation at stimulation rates of up to 25 Hz with an 11-cm water-cooled round coil held flat on the scalp and centered over 15 different positions on each side of the scalp. Stimulation was delivered in 10-s trains while the patients counted aloud. Stimulation centered over inferolateral frontal cortex (D5 or D7 from the standard electrode position nomenclature for closely spaced electrodes) induced reproducible speech arrest in all patients and counting errors in three patients when applied at lower intensities. There were no such speech disturbances when magnetic stimulation was applied over the different positions on the right side. The intracarotid amytal test demonstrated left hemispheric language dominance in all patients. In a follow-up study on three subjects (Pascual-Leone, Dhuna and Gates, 1991a), the same authors demonstrated that the speech arrest induced by rapid-rate transcranial magnetic stimulation was most likely not due to effects on the cortical motor representation of the laryngeal muscles recorded by surface electrodes (Fig. 2). More recent and careful studies mapping the motor responses evoked by transcranial magnetic stimulation of the cortex in intrinsic laryngeal muscles recorded by needle electrodes seem to confirm that the sites of induction of speech arrest are different and anterior to those that evoke laryngeal motor responses (Ludlow, Pascual-Leone, Cozens-Hoffman et al., 1993) and unpublished data).

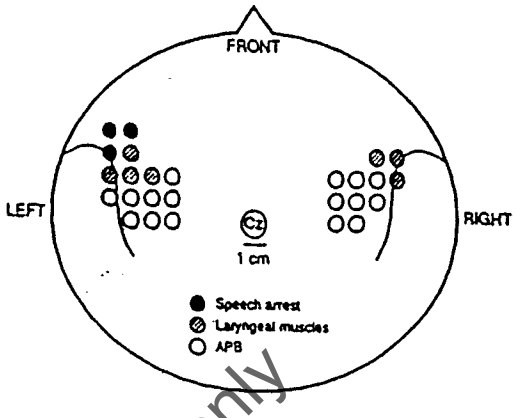

Fig. 2. Schematic map of scalp stimulation sites that led to speech arrest or motor evoked potentials in laryngeal muscles or contralateral abductor pollicis brevis (APB) in a representative subject. Speech arrest was induced with a Cadwell High Speed Magnetic Stimulator equipped with an 8-shaped coil delivering trains of 5 s, at 15 Hz and 120% of subject's motor threshold intensity. Motor evoked responses were recorded with surface electrodes following stimulation with the same stimulator and coil delivering single pulses at 120% of subject's motor threshold intensity.

Other investigators have confirmed the usefulness of repetitive transcranial magnetic stimulation for the study of the language dominant hemisphere. Michelucci, Valzania, Passarelli et al. (1993) studied 12 epileptic patients asked to count aloud while receiving transcranial magnetic stimulation at frequencies of up to 25 Hz, in trains of 10-s duration, and with stimulation intensities of 60–100% of the maximal stimulator output. Repetitive transcranial magnetic stimulation induced speech arrest in 5 of 12 patients. The inability to induce speech arrest in 7 subjects might have been related to their high stimulation threshold due to their concurrent treatment with antiepileptic drugs (Hufnagel, Elger, Marx et al., 1990c). Jennum, Friberg, Fuglsang-Frederiksen et al. (1993) conducted a very careful study with a large number of subjects. They studied 22 epileptic patients, one of which did not tolerate rapid-rate transcranial magnetic stimulation because of the induced muscle contractions. In the other 21 patients, stimulation was applied at 30 Hz for 1 s over several temporal and frontal areas bilaterally while the subjects pronounced words or counted forward or backward. Fifteen patients showed left-

hemispheric speech dominance, two patients showed right-sided speech dominance, and one patient showed bilateral speech representations. These results correlated exactly with the results of the intracarotid amytal test. In the other three patients, magnetic stimulation suggested bilateral speech representation but the intracarotid amytal test demonstrated unilateral speech dominance (left-sided in two cases and right-sided in one).

Transcranial magnetic stimulation in the study of language

Most of our knowledge about the cortical organization of language is derived from direct cortical stimulation studies performed on patients undergoing neurosurgical procedures (Ojemann, 1983; Penfield and Roberts, 1959) or from cortical lesion studies (Damasio and Geschwind, 1984). More recently, positron emission tomography (PET) has been used to study language processing in intact humans (Petersen, Fox, Posner et al., 1989). Transcranial magnetic stimulation may allow the study of the cortical organization of language in intact humans with greater temporal resolution than PET and provide information about excitatory or inhibitory influences of different cortical areas.

Claus, Weis, Treig et al. (1993) have studied the effect of rapid-rate transcranial magnetic stimulation of temporal and parietal areas on verbal comprehension in 44 normal volunteers. The results were influenced by the subject's reading strategy. Nevertheless, they were able to show that in right-handed subjects stimulation over the left hemisphere resulted in a significant greater number of verbal comprehension errors. In a series of elegant studies on the effects of stimulation of different cortical areas on the perception and processing of visually presented letters and words, researchers at SUNY Health Science Center in Brooklyn, NY (USA) have illustrated the value of single-pulse magnetic stimulation to study the temporal profile of the activation of different components of the neural network subserving visually accessed language information (for review, see Amassian, Maccabee, Cracco et al., 1989b; Maccabee, Amassian, Cracco et al., 1991). Appropriate stimulation in time over Wernicke's area can induce a significant reduction in word sequencing, while over Broca's area it can induce phonemic and semantic substitutions (Maccabee et al., 1991). In our studies on repetitive transcranial magnetic stimulation of Broca's area, we found that stimulation intensities and frequencies below those required for induction of speech arrest could lead to counting errors (Pascual-Leone et al., 1991c) and phonemic paraphasias in a word generation task (Table 2). These errors are experienced by the subject with great surprise and often with frustration.

Transcranial magnetic stimulation in the study of memory

In studying memory, it would be advantageous to have a safe and reliable technique that could result in a

TABLE 2

Counting errors and phonetic paraphasias induced by repetitive transcranial magnetic stimulation (rTMS) of Broca's area

Subject	Task	rTMS		Subject's performance
		Frequency (Hz)	Intensity (% of motor threshold)	
1	Count aloud	8	12	'...4, 5, 5, 5, 6, 7, ...' '...8, 9, 7, 11, 12, 13,...' '...5, 6, 6, 7, 8, ...'
2	Generate words beginning with the letter 'j'	10	120	'...jump, joke, giant, jelly'
3	Generate words beginning with the letter 'f'	10	110	'...fall, farm, phase, field, phone, foooo (and speech arrest)'

'reversible lesion' leading to a temporary and selective 'amnesia' in normal subjects. Rapid-rate transcranial magnetic stimulation appropriately delivered in time and space can transiently block the function of neural networks and may provide such a technique. Single-pulse transcranial magnetic stimulation does not appear to affect memory processing (Bridgers and Delaney, 1989; Bridgers, 1991; Ferbert et al., 1991) except in the context of visual scanning (Beckers and Hömberg, 1991). However, in most of these studies, magnetic stimulation was not delivered concurrently with the to-be-remembered material making it difficult to determine if any association existed between transcranial magnetic stimulation and alterations in memory processing. In any case, repetitive stimulation may be necessary to interrupt processing in the stimulated area long enough to make effects on higher order cognitive processes such as memory detectable.

Grafman, Pascual-Leone, Alway et al. (1994) used rapid-rate, repetitive transcranial magnetic stimulation for the non-invasive study of verbal recall in five right-handed subjects. Recall followed immediately after presentation of a 12-word list. Transcranial stimulation was applied in trains of 500-ms duration, 20 Hz, and 120% of the subject's motor threshold intensity to different bihemispheric scalp positions at different latencies after each to-be-remembered word was presented. In all subjects, recall was significantly diminished only after left mid-temporal and dorsofrontal stimulation at 0 ms and 250 ms latencies. Forgetting occurred primarily for words presented at the beginning of the list (primacy effect). It appears, that appropriately delivered in time, rapid-rate transcranial magnetic stimulation of mid-temporal and dorsofrontal sites of the dominant hemisphere can induce transient recall deficits and may be useful as a non-invasive tool for the study of verbal memory processes. However, the choice of the task and the stimulation site, time, and settings seem to be essential in order to induce memory deficits. Hufnagel, Claus, Brunhoelzl et al. (1993) failed to show any effects of rapid-rate transcranial magnetic stimulation on immediate repetition of digits and reproduction of a spatial pattern. Both of these tasks rely exclusively on short-term memory processes while the task used by Grafman et al. (1994) requires storage and retrieval from longer-term memory storage and the effects found were limited to a short time window.

Magnetic stimulation studies of visual processing and visual attention

Subjective photic sensations (phosphenes) were among the first effects of magnetic brain stimulation described in the early 1900s but arose mostly from stimulation of the retina rather than stimulation of the visual cortex (see the section on the history of transcranial magnetic stimulation). However, transcranial magnetic stimulation of the occipital cortex can also evoke phosphenes within the visual field (Marg, 1991). These phosphenes are generally described as flashes of light which subjectively do not last longer than a fraction of a second. The topographic distribution of these white, undifferentiated phosphenes in the visual field depend on the exact localization of the stimulation coil over the occipital area and on the direction of current induced in the brain (Meyer, Diehl, Steinmetz et al., 1991). Such studies explore the functional organization of the different portions of the visual fields in the calcarine fissure. Brief trains of rapid-rate transcranial magnetic stimulation are more likely to evoke phosphenes in sighted, normal volunteers than single pulse stimulation. When trains of five magnetic pulses at 10 Hz and high intensity are applied to different occipital areas, the subjects report phosphenes of different characteristics. Stimulation of the occipital pole seems to evoke white, undifferentiated phosphenes, while stimulation of parieto-occipital areas seems to preferentially evoke phosphenes with a motion component and stimulation of infero-lateral occipital areas seems to preferentially evoke colored phosphenes (Pascual-Leone et al., unpublished data). For example, after stimulation of the appropriate parieto-occipital site, the subject might report seeing a flash of light that seemed to move from the right of the visual field to the center. After stimulation of the appropriate infero-lateral occipital site, the subject might report seeing a green, red, or blue flash of light in a certain spot of the visual field. These findings correlate with the notions of parallel processing of motion

and color attributes of visual stimuli derived from animal experiments and human PET experiments (Zeki, Watson, Lueck et al. 1991). In this fashion, transcranial stimulation may be used in the study of functional organization of the visual cortical system in humans.

Transcranial magnetic stimulation not only has excitatory effects but it can also transiently disrupt the function of a localized group of neurons. Amassian and colleagues pioneered the use of this latter effect in the study of visual cortex. When applied to the occipital lobe at appropriate intensity, transcranial magnetic stimulation can block the detection of visual stimuli presented approximately 100 ms prior to an occipital transcranial magnetic stimulus (Fig. 3A) (Amassian, Cracco, Cracco et al., 1988). Thus, transcranial magnetic stimulation can be used to demonstrate that by 120–160 ms, the information required for visual stimulus recognition is relayed from the calcarine cortex to extrastriatal areas (Maccabee et al., 1991).

The topographical organization of the visual cortex can be demonstrated by shifting the magnetic stimulation coil laterally or rostrally which results in suppression of the contralateral or caudal-most item of a string respectively (Maccabee et al., 1991; Meyer et al., 1991) When two letter trigram stimuli of appropriate luminance are presented in succession so that classical backward masking of S1 (the target) by S2 (the mask) occurs, a transcranial magnetic stimulus delivered 80–100 ms after S2 results in suppression of S2 but unmasking of S1 (Amassian et al., 1989a; Maccabee et al., 1991). Transcranial magnetic stimulation can therefore demonstrate the time course of the transfer of stimuli from striate to extrastriate levels. This unmasking phenomenon can be used to track information flow from visual cortex to higher cortical centers (e.g. arcuate gyrus or the inferior temporal lobe). Applied to parieto-occipital areas, transcranial magnetic stimulation can interfere with motion detection (Beckers and Hömberg, 1992a) and applied to inferior occipito-temporal areas, it can disrupt color perception (Maccabee, Amassian, Cracco et al., 1989) thus allowing for the study of parallel processing of physical attributes of visual objects in humans (Beckers and Hömberg, 1992b).

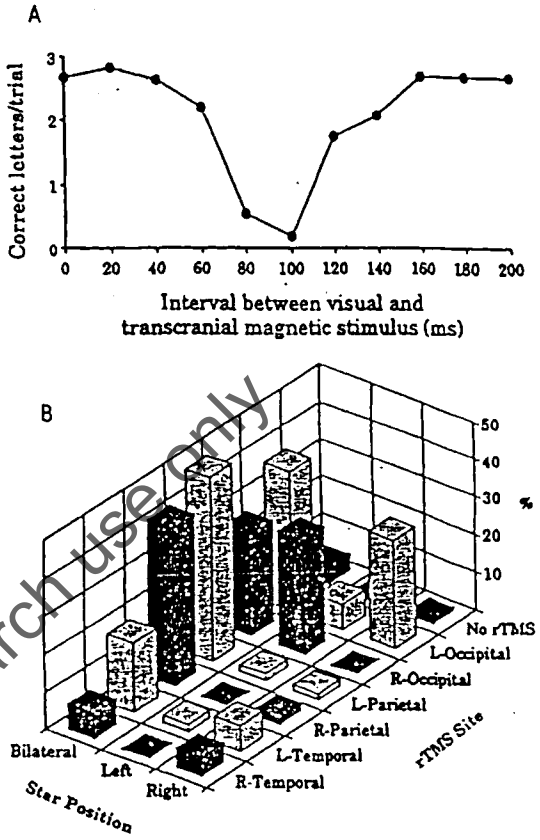

Fig. 3. (A) Effect of transcranial magnetic stimulation of the occipital cortex on detection of three letters horizontally displayed. Data shown represent mean values for three subjects according to the interval between the visual and the transcranial stimulus. This figure is redrawn from data from Amassian et al. (1988). (B) Effect of transcranial magnetic stimulation of occipital, parietal, and temporal areas on single and double simultaneous visual stimulation. three-dimensional bar graph for the mean number of errors (% of total responses) in six subjects according to visual stimulus type and transcranial stimulation site. Reproduced from Pascual-Leone et al. (1994) with permission from the authors.

So far, attempts to apply single pulse magnetic stimulation to the study of higher order visual processing and visual attention have been unsuccessful. Repetitive, rapid-rate stimulation rather than single pulses may be necessary to interrupt processing in the stimulated area long enough to make the effects detectable. Amassian et al. (1990a) have shown that a consecutive train of three magnetic stimuli given 70, 143 and 216 ms following a brief alphabetic trigram stimulus elicits a significant reduction in letter per-

ception. These results contrast with the absence of suppression when a single magnetic pulse is given 70 or 143 ms following presentation of the alphabetic trigram and suggest that the first transcranial stimulus delays the processing of information by the visual cortex but requires supplemental repetitive stimulation to prevent it.

Rapid-rate, repetitive transcranial magnetic stimulation can also be used for the non-invasive study of visual attention in humans (Pascual-Leone, Gomez-Tortosa, Grafman et al., 1994). Six right-handed volunteers completed 8 blocks of 20 single and 10 double visual stimulation trials. The visual stimuli were either a single asterisk on the right or the left of a computer screen or the two asterisks presented simultaneously. The subject had to respond by pressing the right or left response key or both keys simultaneously. During six of the blocks, focal transcranial magnetic stimulation was applied in trains of five pulses at 25 Hz and 115% of the subject's motor threshold intensity to O1, O2, P3, P4, T5 or T6. Occipital stimulation led to a significant number of misses of the contralateral asterisk regardless of whether single and double stimulation was presented. Parietal stimulation did not induce misses of single stimuli, but led to a significant number of misses of the contralateral asterisk in the double stimulation condition. The effects of temporal stimulation were less well defined. These results suggest that rapid-rate transcranial magnetic stimulation to the occipital lobe causes a sensory detection block while stimulation of the parietal lobe can induce a spatial hemi-inattention with selective extinction of contralateral visual stimuli during double simultaneous stimulation (Fig. 3B).

Magnetic stimulation studies of somatosensory perception

Processing of somatosensory stimuli can be studied with transcranial magnetic stimulation in a similar fashion to that outlined above for studies of visual perception. Transcranial magnetic stimulation of the sensori-motor cortex can occasionally trigger somatotopically organized paraesthesias (Amassian, Somasundaram, Rothwell et al., 1991c; Cohen, Topka, Cole et al., 1991). In addition, single pulse transcranial magnetic stimulation of the sensorimotor cortex appropriately timed in relation to an electric stimulus to a finger of the contralateral hand can block the detection of the sensory stimulus (Cohen, Bandinelli, Sato et al., 1991). These studies can be used to investigate the effects of peripheral nerve and spinal cord injury (Cohen et al., 1991), transient deafferentation (Brasil-Neto, Cohen, Pascual-Leone et al., 1992b; Brasil-Neto, Valls-Solé, Pascual-Leone et al., 1993), and skill acquisition (Pascual-Leone and Torres, 1993) on the somatosensory representation of the affected body parts.

Transcranial magnetic stimulation in the study of behavioral aspects of motor control

Different cortical areas are involved in the learning, planning, execution, and correction of movements. Their coordinated, orderly function is necessary for normal human motor performance. Single pulse magnetic stimulation allows the study of the pyramidal tract and the primary motor cortex (Rothwell et al., 1991) but only limited probing into the function of other areas involved in motor control, such as supplementary motor cortex or dorsolateral frontal lobe (Amassian, Cracco, Maccabee et al., 1991a). Transient, selective suppression of the function of different motor areas by trains of magnetic stimuli will allow the study of their role in simple movements, complex movements, bilateral movements, delayed responses, and motor learning. This insight would increase our understanding of pathological conditions of abnormal motor control such as apraxia, dyskinesias, or motor learning disabilities.

Rapid-rate transcranial magnetic stimulation can be use to study the role of the prefrontal cortex in perseveratory motor behavior in normal humans performing a motor sequencing task (Pascual-Leone et al., unpublished observations). Supplementary motor area stimulation at high intensity slows down the performance but has no effect on the motor alternation during the sequence. However, stimulation of the dorsolateral frontal cortex disrupts the motor alternation, induces motor perseverations, or even leads to a complete col-

lapse of the motor sequence despite not affecting the quality or fluency of the individual movements.

Rapid-rate transcranial magnetic stimulation can also be used in conjunction with a serial reaction time task (Nissen and Bullemer, 1987) to demonstrate the critical role of the dorsolateral frontal cortex in procedural learning (Pascual-Leone et al., unpublished observations). Subjects were seated in front of a computer screen and a keyboard with four marked response keys. An asterisk appeared in one of four positions that were horizontally spaced on the screen and aligned above the response keys. The subjects had to press with one finger the key aligned with the asterisk that appeared as fast as possible. They were only allowed to use the right hand to respond. The asterisk did not disappear until the correct button was pushed, upon which the next stimulus appeared following a 500-ms delay. Each test consisted of 50 sets of 10 trials. In the first 40 sets, the sequence of asterisk positions was the same, i.e. a 10-trial sequence of asterisk positions repeated itself 40 times. The subjects were not told that a repeating sequence was being presented. In the last 10 sets of trials, the sequence of asterisk positions was random. In this design, procedural knowledge may occur without development of declarative knowledge of the sequence and is indexed by the progressive shortening of response times during the sets with a repeating sequence, and a rebound lengthening of response time in the random sets (Nissen and Bullemer, 1987; Willingham, Nissen and Bullemer, 1989). Transcranial magnetic stimulation of the left dorsolateral frontal area at 5 Hz and 120% of the subject's motor threshold intensity does not interfere with the response accuracy but abolishes the progressive shortening of response times, i.e. the development of procedural knowledge of the sequence (Fig. 4).

Another approach to study the neural network devoted to movement planning and execution is to investigate the effects of different interventions on the amplitude and latency of motor potentials evoked in contralateral muscles by transcranial magnetic stimulation of the motor cortex. Interventions that alter the level of excitability at the spinal level can obviously influence the amplitude of the motor potentials evoked by transcranial magnetic stimulation of the motor cortex. This can be achieved by holding a certain level of static contraction of the target muscle (Hess, Mills and Murray, 1986; Helmers, Chiappa, Cros et al., 1989; Hufnagel, Jaeger and Elger, 1990d; Ackermann,

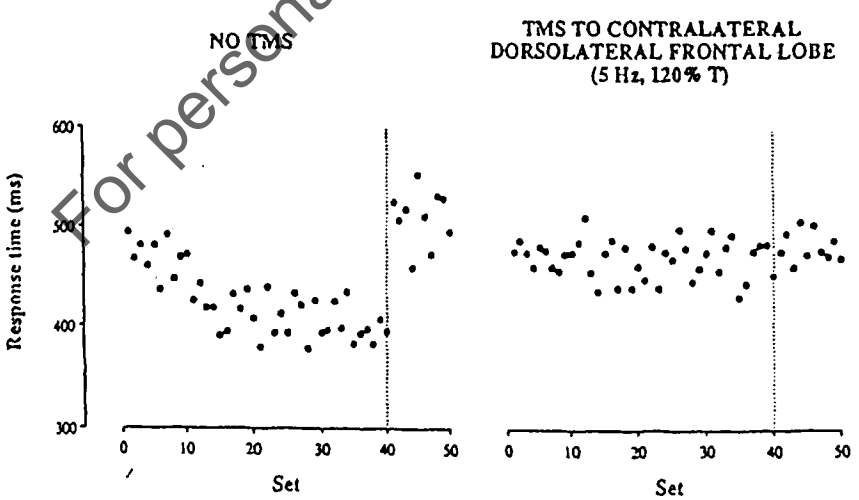

Fig. 4. Effect of transcranial magnetic stimulation (TMS) of the dorsolateral frontal cortex on response time in a serial reaction time task. Data shown represent mean response time values for a representative subject across the 50 sets of trials. The lack of progressive shortening of response times across the first 40 sets of trials and the absence of a rebound delay in response time in the last ten sets indicate the lack of procedural learning of the repeating sequence (see text for details).

Scholz, Koehler et al., 1991; Thompson, Day, Rothwell et al., 1991) or by delivering a peripheral mechanical (Claus, Mills and Murray, 1988) or electric stimulus (Date, Schmid, Hess et al., 1991) at the appropriate time before the transcranial magnetic stimulus. Modulation of the amplitude of motor evoked potentials can also be documented depending on the task that requires the activation of the target muscle (Datta, Harrison and Stephens, 1989; Flament, Goldsmith, Buckley et al., 1993), in the time leading up to a voluntary response (Starr, Caramia, Zarola et al., 1988; Caramia, Pardal, Zarola et al., 1989; Pascual-Leone, Valls-Solé, Brasil-Neto et al., 1991e) (Fig. 5A), or even by simply having the subject *think* of activating the target muscle (Fig. 5B). These kind of studies provide information about task-dependent cortical mechanisms that modulate the cortico-spinal activation in preparation of and during different movements. Studies using pairs of transcranial magnetic stimuli rather than single stimuli may provide further insight into the mechanisms regulating this balance of cortical excitation and inhibition (Claus, Weis, Jahnke et al., 1992; Valls-Solé, Pascual-Leone, Wassermann et al., 1992).

Reaction time studies

Single pulse transcranial magnetic stimulation of the motor cortex can delay or shorten simple reaction time depending on the stimulation intensity and the interval

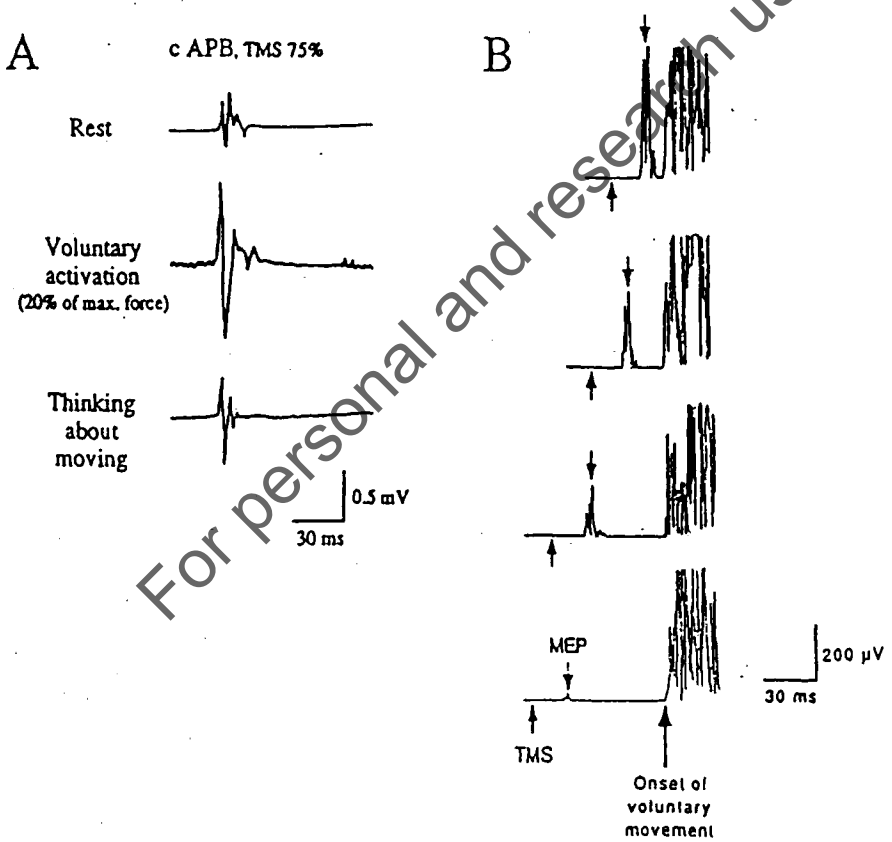

Fig. 5. (A) Effect of static voluntary contraction of the contralateral abductor pollicis brevis (cAPB) and thinking about moving the contralateral thumb on the amplitude and latency of motor evoked potentials (MEP) induced by transcranial magnetic stimulation (TMS) of the motor cortex. (B) Amplitude of the motor evoked potentials (MEP) induced by a transcranial magnetic stimulus (TMS) to the contralateral motor cortex as a function of the timing of the transcranial stimulus in relation to the eventual onset of the voluntary response in a simple reaction time paradigm. Reproduced from Pascual-Leone et al. (1991) with permission from the authors.

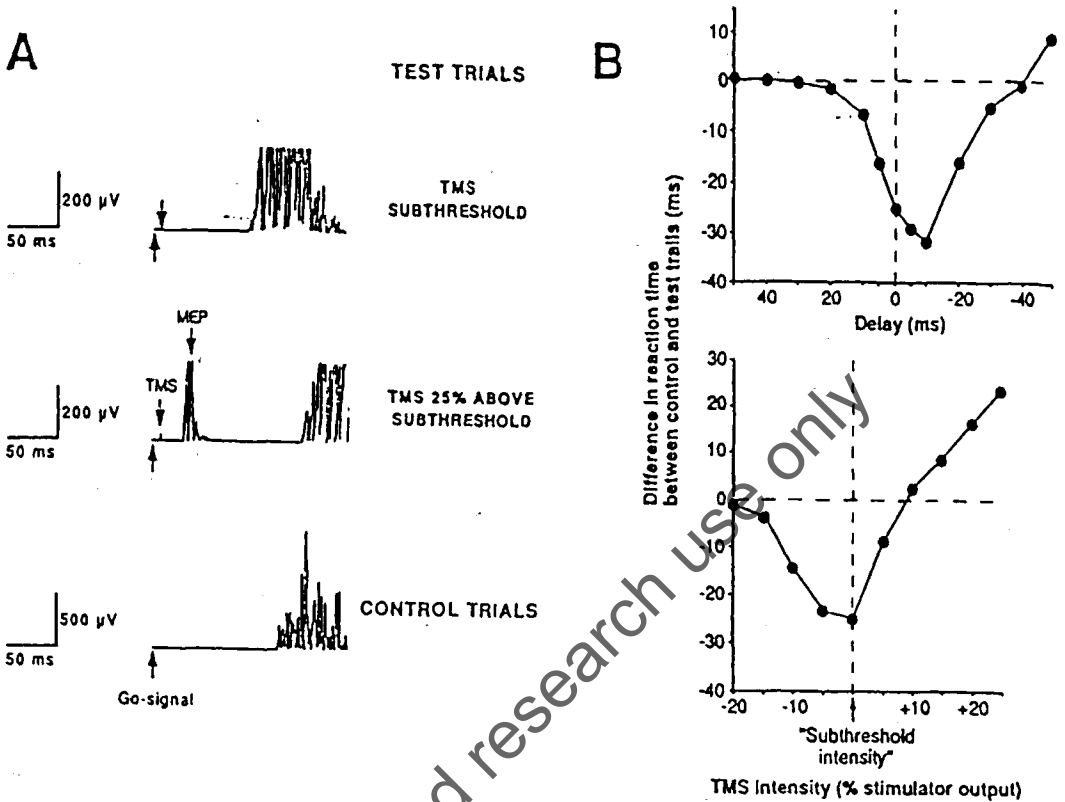

Fig. 6. Effect of transcranial magnetic stimulation (TMS) of the motor cortex on elbow flexion reaction time according to stimulation intensity and interval between the magnetic stimulus and the go-signal (delay). Subthreshold intensity refers to the intensity at which no biceps motor evoked potential was recorded (sensitivity 50 μV/division) in any of five trials with the subject at rest when transcranial magnetic stimulation was delivered over the ideal scalp position for biceps activation. (A) Representative examples of the EMG recorded in one subject. (B) Graphs of the mean difference in reaction time in trials without (control) and with (test) magnetic stimulation in five subjects. Modified from Pascual-Leone et al. (1991) with permission from the authors.

between transcranial stimulus and the go-signal (Day, Rothwell, Thompson et al., 1989b; Pascual-Leone et al., 1991a,b).

In addition, using an intensity of transcranial magnetic stimulation of the motor cortex that will not produce any motor evoked potentials in contralateral muscles at rest, but will evoke a motor potential when there is voluntary activation, Starr et al. (1988) showed that in a reaction time situation stimulation close to movement onset produces a response even though there is still no voluntary EMG activity. A small response first appears about 80 ms before EMG onset and grows in magnitude closer to onset (Fig. 5A). This method divides the reaction time into two periods. In the first period, the motor cortex remains 'inexcitable'. In the second period, the cortex becomes increasingly 'excitable' as it prepares to trigger the movement. This allows the study of the time-course of motor cortex facilitation during the preparation to execute a response in simple (Pascual-Leone, Brasil-Neto, Valls-Solé et al., 1991d) and choice reaction time paradigms (Pascual-Leone and Hallett, 1992). In a simple reaction time paradigm, when a single stimulus is used as go-signal and the expected movement is described completely in advance, this progressive increase in motor system excitability leading up to the voluntary movement is restricted to the cortical projections to muscles involved in the task. In a choice RT paradigm, when one of several possible movements will be requested from the subject who has to

distinguish between different sensory stimuli and respond appropriately to them, premovement facilitation begins before discrimination of the go-signal is completed. The subject seems to prepare simultaneously to execute all the possible responses and commit to one just before the movement, when go-signal evaluation is completed (Pascual-Leone and Hallett, 1992). These studies provide important information about the mechanisms involved in motor programming and response execution and support the notion that in the choice reaction time condition, there must be substantial degree of parallel processing of go-signal evaluation and response initiation.

Single transcranial magnetic stimuli appropriately applied in time and space can also influence a subject's choice of a movement although the subject perceives his/her movement as voluntary (Ammon and Gandevia, 1990; Brasil-Neto, Pascual-Leone, Valls-Sole et al., 1992d). These results show that transcranial magnetic stimulation can influence motor behavior and allow the investigation of the roles of different cortical structures in the planning of voluntary actions.

Studies of cerebral plasticity: neurophysiological correlates of acquisition of new skills and learning

Fine motor skill acquisition implies the development and implementation of 'translation mechanisms' to convert factual knowledge into action. The ability to activate the necessary neural structures to extract the required information from a given task and execute its demands constitutes a skill that can be refined with practice. Presumably, the nervous system has to be modified to yield such changes in ability. Throughout life specific molecular, biochemical, electrophysiological, and structural changes take place in central nervous system neurons and neuronal networks in response to activity and behavior (Kaas, 1991). This experience-dependent plasticity leads to the required modifications in neural structure that enable us to learn new skills and form memories (Kaas, 1991; Merzenich, Recanzone, Jenkins et al., 1990). Several studies have established the utility of transcranial magnetic stimulation in the study of cortical plasticity during the adaptation to and recovery from peripheral and central nervous system lesions in humans (for review see Cohen, Roth, Wassermann et al., 1991). Therefore, it is reasonable to hypothesize that transcranial magnetic stimulation will also be useful for the study of plastic central nervous system changes associated with learning.

A first approach is to study plastic changes in the central nervous system of subjects with a highly specialized, overlearned skill. We have studied the sensorimotor representation of the reading finger of blind, proficient Braille readers (Pascual-Leone et al., 1993a; Pascual-Leone and Torres, 1993). Subjects and controls were matched for age and number of years of blindness. Subjects had learned Braille at age 8–14 years and used it daily for 5–10 h. Controls had not learned Braille until age 17–21 years and used it daily for less than 1 h. Compared with the results obtained from the non-reading fingers and homologous fingers of blind controls, detection of an electric stimulus applied to the reading fingers was blocked by transcranial magnetic stimulation of the somatosensory cortex over a larger contralateral scalp area and during a longer time window. In addition, topographic somatosensory evoked potential mapping demonstrated a larger area of peak amplitude for several cortical components of the potentials evoked from the reading fingers (Fig. 7A). We also performed detailed mapping of the motor cortical areas targeting the first dorsal interosseus (FDI) and the adductor digiti minimi (ADM) bilaterally in Braille readers and blind control with focal transcranial magnetic stimulation (Fig. 7B). Motor threshold of subjects and controls were similar. In the controls, motor representations of right and left FDI and ADM were not significantly different. In the subjects, however, the representation of the FDI in the reading finger was significantly larger than that in the non-reading finger or in either finger of the controls. Conversely, the representation of the ADM in the reading hand was significantly smaller than that in the non-reading hand or in either hand of the controls. These results suggest that the cortical representation for the reading finger in proficient Braille readers is enlarged at the expense of the representation of other fingers. These plastic changes might be the consequence of the heavy differential sensory input and

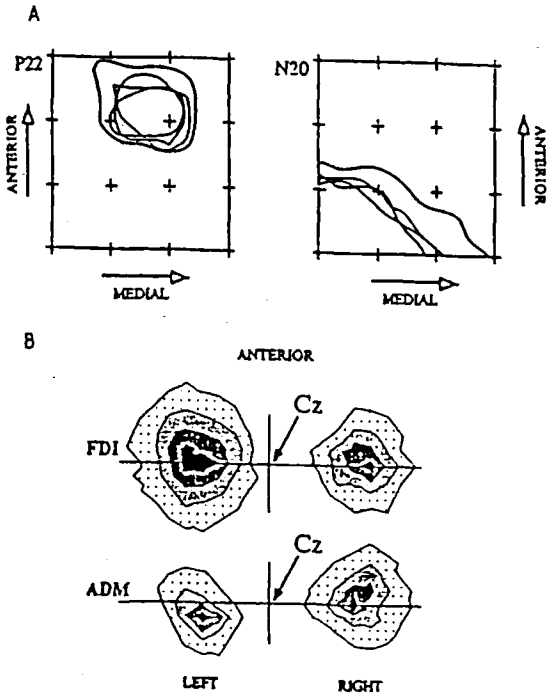

Fig. 7. (A) Superposition of the grand average scalp areas for the N20 and P22 components of the somatosensory evoked potentials (SEPs) after stimulation of the reading finger (heavy line) and the non-reading finger of Braille readers and the control fingers. From each topographic SEP map we calculated the scalp areas from which each component was recorded with an amplitude of ≥70% of the maximal amplitude in each trial. Grand averages were calculated from three trials in 10 Braille readers and 10 controls. Modified from Pascual-Leone and Torres (1993) with permission from the authors. (B) Motor output maps for contralateral first dorsal interosseous (FDI) and adductor pollicis brevis (ADM) muscles in a representative Braille reader. The contours express the extend of the areas that led to motor evoked potentials of ≥80%, ≥60%, ≥40% and ≥20% of the maximal amplitude response for each muscle when applying stimulation at an intensity of 130% of motor threshold. This subject used the right index finger as reading finger. Note the larger left-sided scalp area targeting the (right) FDI and the smaller left-sided area targeting the (right) ADM. Modified from Pascual-Leone et al. (1993a) with permission from the authors.

motor demand on the reading finger and may represent the substrate of the acquisition of the Braille-reading skill.

In a second series of experiments we have explored the changes in motor cortical representation occurring in the course of the acquisition of a new skill (Pascual-Leone, Cohen, Dang et al., 1993c, Pascual-Leone, Dang, Cohen et al., 1994a). Subjects were taught to perform a five-finger exercise on a piano keyboard with one hand. They were instructed to attempt to perform the sequence of finger movements fluently, without pauses, and without skipping any key, while paying particular attention to keeping the interval between the individual key presses constant and the duration of each key press the same. A metronome gave a rhythm of 60 beats/min which the subjects were asked to aim for. The subjects were studied on five consecutive days and each day they had a 2-h practice session followed by a test. The test consisted of the execution of 20 repetitions of the five-finger exercise and was eventually analyzed for the exact sequence of key presses, the interval between keys, the duration and the velocity of each key push. Following each test, the subjects were given feedback about their performance and tips about how to improve. Before the first practice session on the first day, focal transcranial magnetic stimulation was used to map the motor cortical areas targeting long finger flexors and extensors bilaterally. Thereafter, mapping was repeated daily following a 20–30 min rest after the test session.

Over the 5 days of the study, all subjects showed great improvement in their playing skill (Fig. 8A). By the fifth day, the number of errors in the sequence of key presses decreased markedly, and the variability of the interval between key presses decreased in all subjects as illustrated by the narrowing of the standard deviation. At the same time, the threshold for activation of the finger flexors and extensors by transcranial magnetic stimulation to the contralateral scalp decreased steadily over the course of the five training days in all subjects but only for the hand being trained, and, even taking this change in threshold into account, the size of the cortical representation for both muscle groups increased (Fig. 8B).

To ensure that the changes found were associated with the acquisition of a new skill, rather than simply with the increased use of one hand, we studied a control group of age-matched subjects who were not taught the five-finger movement exercise, rather, they were asked to spend 2 h each day at the piano keyboard playing whatever they wanted using only one hand. Therefore, the daily use of the hand at the piano was similar in both subject groups, but the test sub-

sprouting, and unmasking of previously existing connections. The excitability of muscles immediately proximal to ischemic anesthesia of the forearm increases in minutes and returns to baseline levels following termination of ischemia (Brasil-Neto et al., 1992b). This rapid modulation takes place intracortically, without a change in spinal/segmental level excitability (Brasil-Neto et al., 1993). The rapid time course in the modulation of the motor outputs, by which a certain region of motor cortex can reversibly increase its influence on a motoneuron pool, is most compatible with unmasking of previously existing connections, perhaps due to disinhibition at cortical level (Jacobs and Donoghue, 1991). Such flexible, short-term modulation might represent the first stage leading up to longer-term plastic changes associated with structural changes in the establishment of new procedural knowledge and recovery of function.

Conclusions

Transcranial magnetic stimulation allows the non-invasive stimulation of the human cortex. It is a safe technique if appropriate precautions are taken. Transcranial magnetic stimulation, either in single pulses or as trains of variable frequency and duration, can be used in the study of a variety of cognitive functions and it can provide complementary information to the one obtained using neuropsychological tests, evoked potentials, magnetic resonance imaging or positron emission tomography. Transcranial magnetic stimulation is a promising tool for cognitive neuroscience and its applications are only limited by the design of the appropriate tasks and experiments.

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