

Study and Modulation of Human Cortical Excitability With Transcranial Magnetic Stimulation

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Summary: Transcranial magnetic stimulation (TMS) can be applied in different paradigms to obtain a measure of various aspects of cortical excitability. These different TMS paradigms provide information about different neurotransmitter systems, enhance our understanding about the pathophysiology of neuropsychiatric conditions, and in the future may be helpful as a guide for pharmacological interventions. In addition, repetitive TMS (rTMS) modulates cortical excitability beyond the duration of the rTMS trains themselves. Depending on rTMS parameters, a lasting inhibition or facilitation of cortical excitability can be induced. These effects can be demonstrated neurophysiologically or by combining rTMS with neuroimaging techniques. The effects do not remain limited to the cortical area directly targeted by rTMS, but affect a wider neural network transynaptically. Modulation of cortical excitability by rTMS may in the future be useful not only as a research tool but also as a therapeutic intervention in neurology, psychiatry, and neurorehabilitation. **Key Words:** Repetitive transcranial magnetic stimulation—Neuroimaging—Cortical excitability.

Transcranial magnetic stimulation (TMS) allows noninvasive stimulation of human cortex. The safe use of TMS requires adherence to certain guidelines and precautions (Wassermann, 1998) since side effects, in particular the induction of a seizure, are possible. However, if recommended safety guidelines are followed, TMS, even repetitive TMS (rTMS) at rates ≤ 25 Hz, appears to be a safe tool that can yield new insight into human cortical physiology in health and disease (Pascual-Leone et al., 1993; Pascual-Leone and Wassermann, 1996; Wassermann et al., 1996; Wassermann, 1998).

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Currents induced in the brain by TMS 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., 1991; Saypol et al., 1991). This results in preferential activation of neural elements oriented horizontally, i.e., parallel to the cortical surface (Amassian et al., 1987, 1989, 1990; Day et al., 1987, 1989). Most of the intracortical horizontally oriented neural elements are interneurons. Preferential activation of such interneurons would support the hypothesis that, at least at low-stimulation intensities, TMS is more likely to activate pyramidal cells transynaptically (Amassian et al., 1987, 1989, 1990; Day et al., 1987, 1989). This notion is not unchallenged (Edgley et al., 1990, 1997) and is certainly highly dependent on stimulation intensity, coil orientation, sulcal pattern, conductivity of neighboring tissue, and orientation of nerve fibers (Maccabee et al., 1993). Nevertheless, the effects of TMS on human cortex apparently are highly

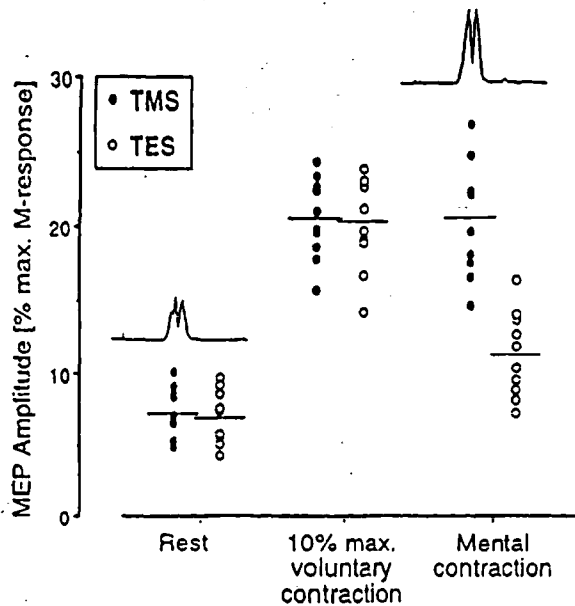


FIG. 1. Modulation of the amplitude of motor evoked potentials (MEP) to transcranial magnetic stimulation (TMS) (solid circles) or transcranial electric stimulation (TES) (open circles) with voluntary physical or mental contraction of the target muscle. Individual results of 10 MEP recorded in each condition in a representative normal subject. Two examples of rectified MEP to TMS at rest and with mental contraction of the target muscle are shown.

dependent on cortical excitability and TMS effects evidently provide a faithful measure of excitability in the targeted cortex and its connections.

When TMS is applied to the motor cortex at appropriate stimulation intensity, motor evoked potentials (MEP) can be recorded in contralateral extremity muscles. The amplitude of the MEP is not only dependent on TMS intensity, but is also greatly influenced by factors that affect corticospinal excitability. For example, voluntary contraction of the target muscle enhances excitability at the spinal level and facilitates the responses to TMS (Hess et al., 1986; Thompson et al., 1991) (Fig. 1). Mental imagery of contraction of the same target muscle results in a similar facilitation of MEP produced by TMS (Fig. 1). In the case of mental imagery, MEP induced by transcranial electric stimulation (TES) are not facilitated, whereas voluntary isometric contraction of the target muscle results in a facilitation of MEP similar to that produced by TMS and TES (Fig. 1). This differential effect of mental contraction of a muscle on responses to TMS and TES suggests an intracortical mechanism.

TMS MEASURES OF 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. Single-pulse TMS can be applied to the motor cortex to determine motor threshold (Fig. 2A). Motor threshold refers to the lowest TMS intensity required to evoke MEP in a target muscle in 50% of trials. Motor threshold is believed to represent a measure of membrane excitability in pyramidal neurons. Support for this claim is derived from changes in motor threshold induced by antiepileptic drugs 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 supra-threshold intensity to the motor cortex to study the induced silent period (Fig. 2B). Silent period refers to the suppression of electromyographic (EMG) activity in the voluntarily contracted target muscle after induction of an MEP. Studies of segmental spinal excitability during this silent period have established the cortical origin of at least the later part of the evoked EMG silence (Fuhr et al., 1991; Triggs et al., 1993; Wilson et al., 1993a; Schnitzler and Benecke, 1994; Brasil-Neto et al., 1995). This postexcitatory cortically generated inhibition can sometimes be observed in the absence of preceding facilitation (silent period without preceding MEP) (Fig. 2B) (Wassermann et al., 1991; Triggs et al., 1993; Catano et al., 1997) and can be shown to have a cortical origin distinct from the optimal site for activation of a given target muscle (Wassermann et al., 1993; Wilson et al., 1993b; Lewko et al., 1996). The balance of cortical glutamatergic (Prout and Eisen, 1994; Faig and Busse, 1996; Yokota et al., 1996), dopaminergic (Priori et al., 1994; Ziemann et al., 1996a), and GABAergic activity (Inghilleri et al., 1993; Ziemann et al., 1995, 1996b, 1996c; Nakamura et al., 1997) appears to play a critical role in the duration of the silent period to TMS.

Single TMS pulses of progressively increasing intensity applied to the motor cortex can be used to generate an input-output curve (Fig. 2C). The resulting modulation of amplitude of MEP to increasing intensity of TMS pulses appears to provide a measure of excitatory feedback to corticospinal efferent output (Valls-Solé et al., 1994) which may be glutamatergically mediated (Prout and Eisen, 1994).

Intracortical excitability can be further studied with the paired-pulse TMS technique (Fig. 2D) (Kujirai et al., 1993). A first, conditioning stimulus is applied, followed at a variable interval by a second, test stimulus. The effects obtained depend on the intensity of the conditioning stimulus, the interval between the stimuli,

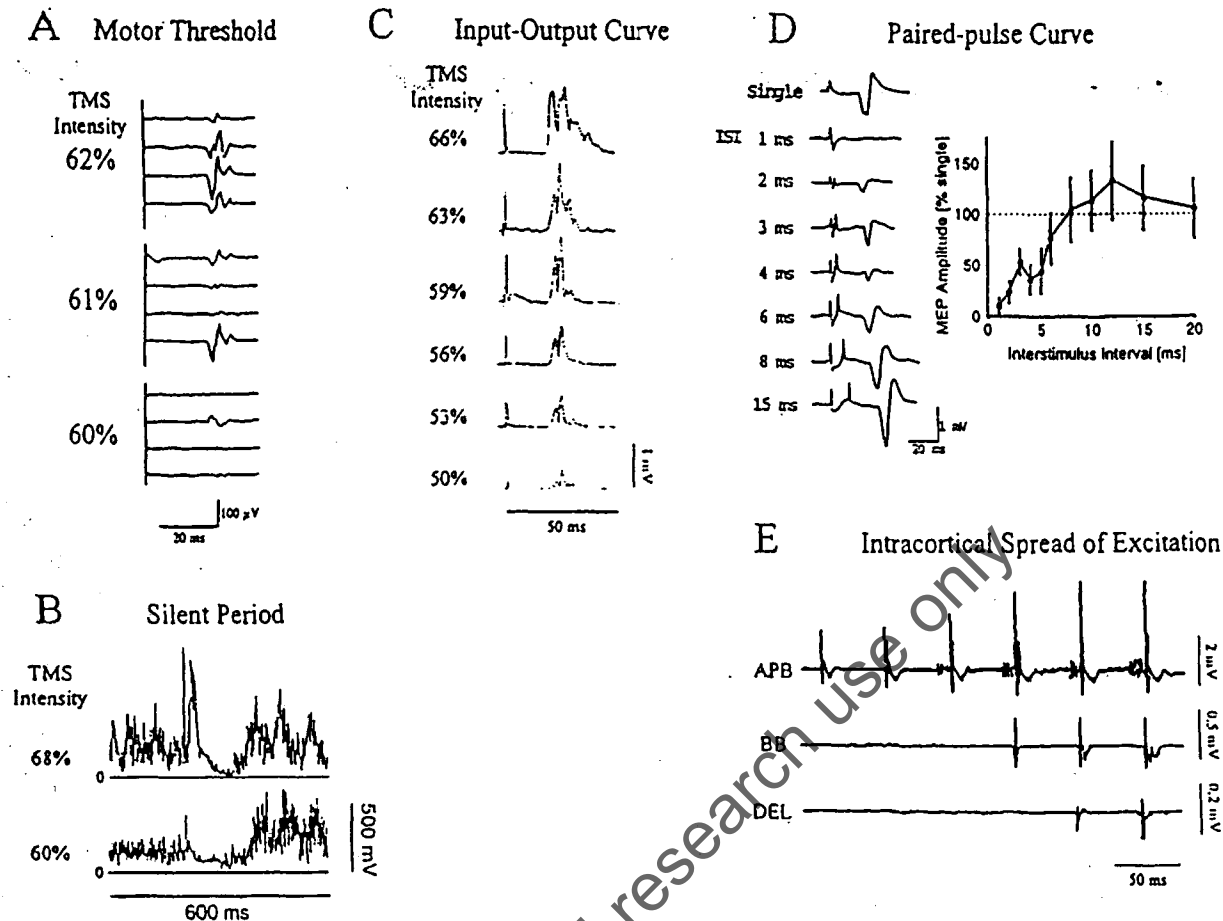


FIG. 2. (A) Representative examples of motor evoked potentials (MEP) induced by transcranial magnetic stimulation (TMS) at decreasing intensities and recorded from the abductor pollicis brevis muscle in a normal volunteer during determination of motor threshold. TMS intensity is expressed as percentage of maximal stimulator output. At an intensity of 62%, MEP were induced in four of four trials. At an intensity of 61%, criterion MEP (50 μ V peak to peak amplitude) were recorded in only two of four trials. At 60% intensity, criterion MEP were recorded in only one of four trials. In practice, we would rely on 10 rather than four consecutively recorded MEP. (B) Representative example of silent periods evoked by TMS at different stimulator output intensities in a normal volunteer. Responses are recorded from the first dorsal interosseus muscle. MEP and postexcitatory silent period at 68% TMS intensity are shown, with a silent period without preceding MEP at 60% intensity. (C) Examples of MEP in an input-output curve in a normal volunteer. Rectified and averaged MEP of a total of 15 single MEP recorded from the thenar musculature at different stimulus intensities are shown. With increasing TMS intensity, there was a progressive increase in MEP amplitude and area, a progressive decrease in latency, and progressive prolongation of MEP duration. (D) Paired-pulse curve to TMS recorded from the first dorsal interosseus muscle of a normal volunteer. The conditioning stimulus was applied at 80% of the subject's motor threshold intensity while the test stimulus was applied at 115%. Left: Representative examples of the recorded MEP are shown for various interstimulus intervals (ISI). Right: The curve of modulation of MEP amplitude depending on ISI is shown for a normal volunteer. MEP amplitude is expressed as percentage from the average amplitude of MEP evoked by the test stimulus alone (% of single). (E) Electromyogram (EMG) recording from the abductor pollicis brevis (APB), biceps brachii (BB), and deltoid (DEL) muscles during a train of repetitive TMS (20 Hz, 120% motor threshold intensity) to the optimal scalp position for activation of the hand muscles showing progressive increase in amplitude of the MEP in the APB and the appearance of MEP in the BB and DEL after four and five stimuli, respectively.

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 ISI (<1 ms) neural time constants of the stimulated elements can be studied; at ISIs of 1–4 ms, interactions between I-wave inputs to corticospinal neurons can be studied; and

at ISIs of 1–20 ms, cortico-cortical inhibitory and facilitatory circuits can be studied. All these effects appear to be cortically mediated (Valls-Solé et al., 1992; Kujirai et al., 1993; 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 suggest that GABAergic and dopa-

minergic mechanisms are involved. Medications that enhance GABAergic activity have been shown to decrease markedly the degree of cortico-cortical facilitation evoked by paired TMS stimuli at ISI of ~8–12 ms (Ziemann et al., 1995, 1996b,c; Inghilleri et al., 1996). Conversely, in Parkinson's disease, the dopamine deficiency is associated with reduced cortico-cortical inhibition at short ISI (<5 ms) (Ridding et al., 1995; Berardelli et al., 1996) and dopaminergic drugs have been shown to enhance cortico-cortical inhibition in normal subjects and patients with Parkinson's disease (Priori et al., 1994; Ridding et al., 1995; Ziemann et al., 1996a; Berardelli et al., 1996). Furthermore, studies suggest that an early phase of facilitation in the paired-pulse curve at ISI of ~3 ms might be related to glutamatergic, excitatory intracortical modulation (Prout and Eisen, 1994; Ziemann et al., 1996d; Detsch and Kochs, 1997).

Finally, the modulation of the MEP recorded in contralateral muscles during rTMS trains provides evidence of the pattern of reentry inhibitory and excitatory pathways (Pascual-Leone et al., 1994c; Jennum et al., 1995). MEP are differentially modulated by rTMS trains at different intensities and frequencies. During trains of rTMS at appropriate intensity and frequency, the phenomenon of intracortical spread of excitation (ISE) (Fig. 2E) was described previously (Pascual-Leone et al., 1994c). ISE most likely is due to 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 that 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 have a profound impact on therapeutic approaches. For example, patients with epilepsy have altered measures of intracortical excitability (Reutens et al., 1993; Jennum and Winkel, 1994; Caramia et al., 1996; Michelucci et al., 1996) that may allow differentiation among forms of epilepsy that cannot be predicted on clinical grounds alone. Different antiepileptic drugs (AEDs), 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 individual patients. Today, the choice of an AED drug for a particular patient with epilepsy often is made empirically, with cost and side-effect profile, rather than expected efficacy or mechanisms of action used as a principal determinant. TMS-derived

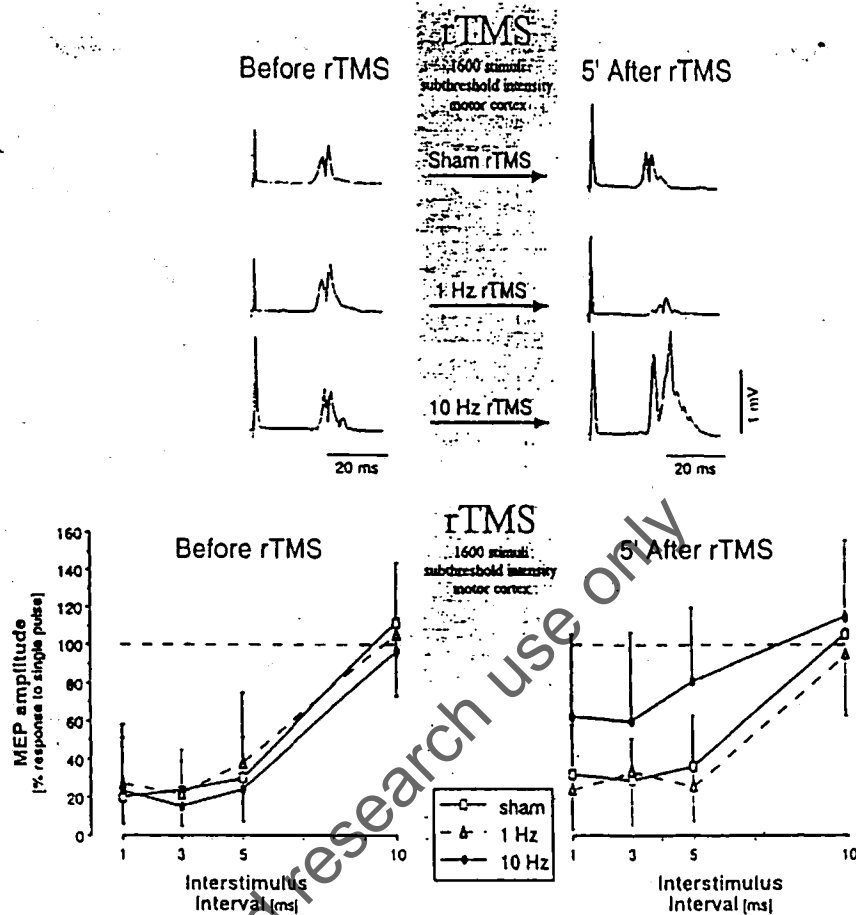
measures of cortical excitability might provide a guide to more pathophysiologically based approaches to neuropharmacology.

MODULATION OF CORTICAL EXCITABILITY WITH TMS

When TMS is applied in trains of multiple stimuli to the same cortical area (rTMS), cortical excitability apparently can be enhanced or decreased in a more sustained fashion depending on stimulation frequency and intensity. The resulting modulation of cortical excitability can be demonstrated for minutes after completion of the rTMS train (Pascual-Leone et al., 1994C). When rTMS is applied to the primary motor cortex at subthreshold intensities so that no MEP are evoked and no changes in spinal excitability are induced, responses to single suprathreshold TMS stimuli can be shown to be suppressed or facilitated depending on the stimulation frequency of the applied rTMS train (Fig. 3) (Chen et al., 1997; Tergau et al., 1997). The mechanisms of this longer lasting modulation of cortical excitability are unclear, but might be related to long-term potentiation (LTP) and long-term depression (LTD). The duration of such excitability shift depends on the duration of the rTMS exposure, i.e., the number of rTMS trains applied and the intertrain interval. Paired-pulse TMS techniques can be used to demonstrate that this excitability shift is due at least in part to intracortical shifts in inhibition and facilitation (Fig. 3) (Tergau et al., 1997). For example, trains of higher frequency rTMS (10 Hz) induce a reduction in intracortical inhibition in most subjects (Fig. 3).

These changes in cortical excitability can be also demonstrated by combining rTMS and functional neuroimaging techniques. For example, we studied the effects of rTMS on the pattern of cortical activation during a simple self-paced motor task as demonstrated by functional magnetic resonance imaging (fMRI) (Fig. 4A) (Pascual-Leone et al., 1997). Blood oxygen level dependent contrast-fMRI studies were obtained while normal volunteers performed a paced fist opening and closing task. Task performance was carefully monitored with EMG and kinematic recording. Images were obtained during the performance of the task: the subject was then removed from the MRI suite and rTMS, either real (1 or 10 Hz) or sham rTMS was applied. Sham rTMS was applied with the stimulation coil angled away from the head to induce a sensation similar to real rTMS in the subject but to avoid induction of any significant currents in the brain. Real rTMS was applied at 90% motor threshold intensity, and sub-

FIG. 3. Neurophysiologic demonstration of the effects of trains of repetitive transcranial magnetic stimulation (rTMS) on cortico-spinal excitability. Trains were applied at subthreshold intensity focally to the motor cortex either at 1- or 10-Hz frequency or as sham rTMS (described in text). Top: Effects of rTMS on the amplitude of single motor unit potentials (MEP). Twenty MEP were recorded (one every 10 s), rectified, and averaged before and 5 min after rTMS. No change was evident after sham rTMS; amplitude and area were decreased after 1 Hz rTMS, and amplitude and area were increased after 10-Hz rTMS. Bottom: Paired-pulse curves for the same subjects before and 5 min after sham rTMS or 1- or 10-Hz rTMS. Cortico-cortical inhibition was significantly reduced at short interstimulus intervals after application of 10-Hz rTMS.



jects received either a single train of 1,600 stimuli at 1 Hz or 20 trains of 8-s duration at 10 Hz (intertrain interval 52 s). Stimulation was aimed at the M1 contralateral to the hand used for the task. Immediately after completion of the rTMS, the subject was repositioned in the MRI scanner by use of scalp markers. A proton density-weighted image was obtained to confirm accurate repositioning before fMRI was repeated during the motor task performance. After 10-Hz rTMS, the activity of M1 was enhanced while caudal supplementary motor area (SMA) cortex showed decreased activation (Fig. 4A). rTMS at 1 Hz resulted in a decrease in M1 activity with increases in SMA and contralateral M1. In all cases, neurophysiologic monitoring allowed documentation of the unchanged motor performance. Sham rTMS induced no change in cortical activity, thus ruling out that changes in fMRI activation were artifactual and unrelated to the rTMS itself. Therefore, rTMS may have modulated cortical activity in M1 depending on stimulation parameters, so that more or less contribution of caudal SMA was required for

proper task performance. Similar approaches with non-motor tasks and stimulation to appropriate cortical regions might shed light on functional networks for cognitive functions.

Applied to other nonmotor cortical areas, rTMS is likely to exert similar modulatory effects on cortical excitability. However, in such cases, EMG recording of MEP cannot be used to document the effects neurophysiologically. In the future, integration of TMS with EEG and neuroimaging techniques may provide a means to investigate such effects in greater detail; e.g., effects of rTMS on regional cerebral blood flow (rCBF) can be sampled by single photon emission computed tomography (SPECT) after intravenous injection of 20 mCi (740 Mbq) of [^{99m}Tc]-bicisate (ethyl cystine dimer, ECD). ECD distributes in the brain in proportion to rCBF soon after injection and then maintains a reasonably stable level for ~4 h. Therefore, the ECD can be injected during application of rTMS and the SPECT images can be obtained later. Using this technique, we studied the effects of rTMS on the left

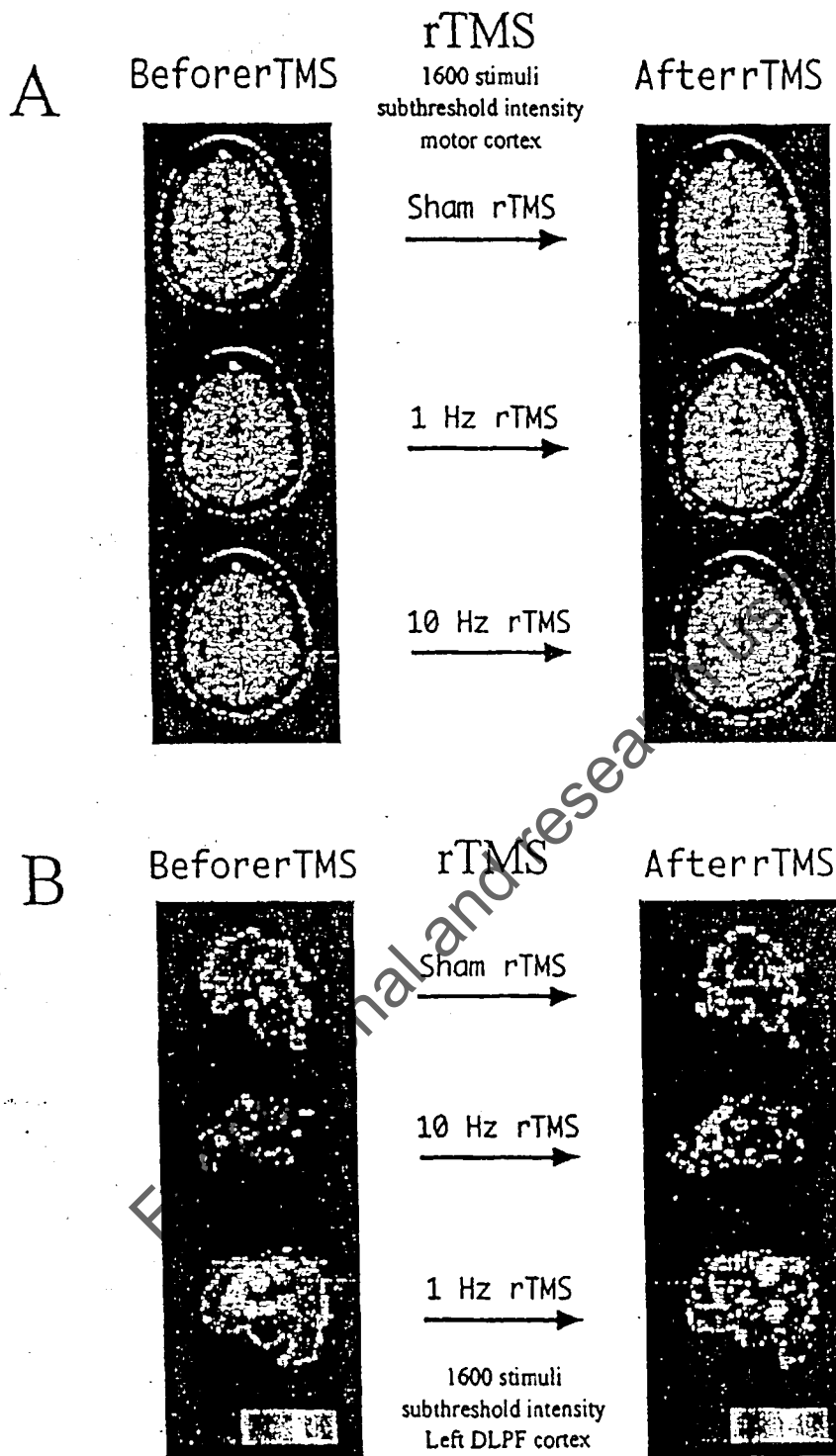


FIG. 4. (A) Functional magnetic resonance images (BOLD) before and after repetitive transcranial magnetic stimulation (rTMS) applied at subthreshold intensity to the motor cortex as sham rTMS or 1- or 10-Hz actual rTMS. Images represent average results from 5 subjects. The fMRI scans were obtained while the subject performed a self-paced fist opening and closing task. Areas of significant activation during task performance were overlaid on an anatomic MRI scan for localization. Repetitive TMS at subthreshold intensity was applied, targeting the primary motor cortex contralateral to the hand with which the subject performed the task. (B) Measures of regional cerebral blood flow at rest made with single photon emission tomography (SPECT) before and after rTMS at subthreshold intensity in 3 patients with medication resistant depression. Repetitive TMS was applied to the left dorsolateral prefrontal cortex in all cases. Images show left lateral view. SPECT images were obtained immediately after rTMS. Differential effects of rTMS depended on stimulation frequency.

dorsolateral prefrontal cortex (DLPFC) in patients with medication-resistant depression. Two studies were conducted in each patient 1 week apart. The first study served as baseline and the second was obtained while rTMS was being applied during the ECD injection. Patients received either sham rTMS or 1- or 10-Hz rTMS. Sham rTMS was applied with the coil angled away from the head to reproduce the subjective sensation of rTMS but to avoid induction of current in the brain. Real rTMS was applied either at 1- or 10-Hz frequency but always at an intensity of 90% of the patient's motor threshold intensity and with 1,600 stimuli in all (single train of 1,600 stimuli for 1-Hz rTMS or 20 trains of 8-s with 52-s intertrain interval for 10-Hz rTMS). These preliminary studies demonstrate that SPECT performed immediately after rTMS can demonstrate the effects of rTMS on CBF and that different effects are indeed demonstrable depending on rTMS parameters. Using a similar approach, Paus et al. (1997) studied the effects of rTMS to the frontal eye field on cortical activity as measured by positron emission tomography (PET). They noted a significant positive correlation between rCBF and the number of TMS pulse trains at the stimulation site and also observed activation in the visual cortex of the superior parietal and medial parietooccipital regions. The pattern of these distal effects is consistent with the known anatomic connectivity of the frontal eye fields. Such studies may shed light on the mechanisms of action of rTMS on nonmotor cortical areas and their distributed functional connectivity without requiring the subject to engage in any specific behavior.

What rTMS parameters are optimal that induce a lasting enhancement or decrease in cortical excitability or how consistent these effects are across subjects is not clear. It might be necessary to individualize rTMS parameters to achieve a consistent increase or decrease in cortical excitability across subjects (Pascual-Leone and Wassermann, 1996); e.g., the same rTMS parameters can result in lasting increase in cortical excitability in 1 subject but decrease in another (Tergau et al., 1997) (Fig. 5). These differential effects appear to be particularly influenced by the frequency of rTMS, and different subjects apparently have different "frequency tuning curves" for rTMS effects on cortical excitability (Tergau et al., 1997) (Fig. 5). Furthermore, the effects probably depend not only on the rTMS frequency and the subject's frequency tuning but also on the context of the application. For example, the same parameters of subthreshold rTMS to the motor cortex when the subject is thinking of flexing the wrist will facilitate MEP to wrist flexors but suppress MEP to

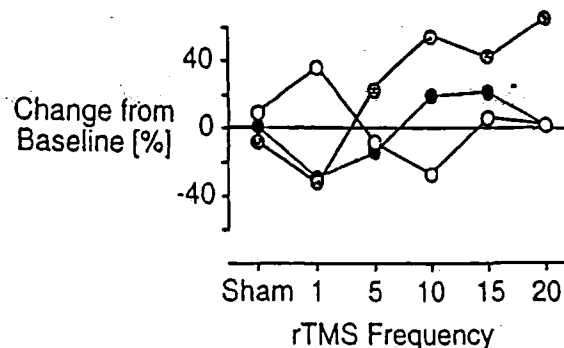


FIG. 5. Modulation of area of the average motor evoked potential (MEP) evoked by 20 single-pulse transcranial magnetic stimulations (TMS) from the abductor pollicis brevis muscle after exposure to subthreshold repetitive TMS (rTMS) at different stimulation frequencies. Results express the change in MEP area after rTMS as compared with area before rTMS (baseline). Results in 3 normal subjects are shown (open, gray, and solid circles). Interindividual results varied markedly.

wrist extensors after the rTMS train. The opposite effect can be demonstrated when the subject is thinking of extending the wrist during application of rTMS.

DOES MODULATION OF CORTICAL EXCITABILITY INDUCED BY RTMS HAVE CLINICAL APPLICABILITY?

Particularly tantalizing is the possibility that modulation of cortical excitability by rTMS might have therapeutic applications in neuropsychiatric illnesses. Given a knowledge of alterations of cortical excitability associated with a given pathology, it might be possible to target the dysfunction and normalize it with rTMS at appropriate stimulation parameters. Much research needs to be done in this area, but results of several studies support this notion.

Most of the research in this area to date has consisted of applying rTMS to patients with major depressive disorder (MDD) (Fig. 6). Patients with MDD frequently have a decreased level of excitability in the prefrontal cortex and enhancement of cortical excitability with rTMS might result in symptomatic improvement. Several different groups of researchers have published preliminary results regarding the antidepressant effects of rTMS. Höflich et al. (1993) applied TMS to 2 depressed patients and noted only minimal beneficial effects. However, they stimulated at 0.3 Hz and with the stimulation coil centered over the vertex, thus affecting both hemispheres simultaneously. In a follow-up study, using the same technique, Kolbinger et al. (1995) studied 15 patients with MDD randomized into three groups of 5 patients: patients

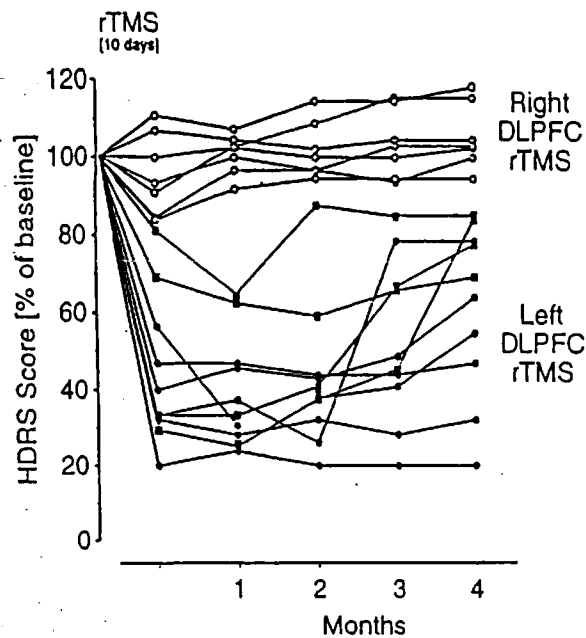


FIG. 6. Effects of repetitive transcranial magnetic stimulation (rTMS) to the right or left dorsolateral prefrontal cortex (DLPFC) on score in the 16-item Hamilton Depression Rating Scale (HDRS) in patients with medication resistant depression. Patients receiving right DLPFC stimulation (open symbols). Patients receiving left DLPFC rTMS (solid symbols). HDRS score was obtained and is plotted at the end of the 10 days of stimulation and monthly thereafter. The difference between the two study groups was marked. Right DLPFC rTMS had no effect, whereas left DLPFC rTMS resulted in marked improvement in HDRS scores and a sustained effect for 4 months in some patients.

who received 250 TMS stimuli at intensities below the motor threshold on 5 consecutive days showed a significant reduction in depressive symptoms. Grisaru et al. (1994), using a nonfocal circular stimulation coil, reported antidepressant effects of rTMS in 10 patients in an "open-label" study. Using focal, high-frequency TMS, George et al. (1995) reported striking beneficial effects of rTMS to the left prefrontal cortex in 4 of 6 patients with medication-resistant depression. However, all these were open studies without control for potential placebo effects of the intervention.

Last year, in the first randomized, multiple cross-over, placebo-controlled trial of rTMS in depression (Pascual-Leone et al., 1996), we studied 17 patients with medication-resistant MDD of the psychotic subtype (DSM-III-R). Sham rTMS and stimulation of different cortical areas were used as controls. Daily rTMS sessions were applied for 5 consecutive days in form of 20 trains of 10-s duration with 1-min intertrain intervals. Stimulation parameters were 10 Hz and 90% of the patient's motor threshold intensity. Only rTMS of DLPFC resulted in a significant decrease in scores on the 21-item Hamilton Depression Rating Scale

(HDRS) and the self-rated Beck Questionnaire (BQ). Eleven of the 17 patients showed marked beneficial effects that lasted ~2 weeks. None of the subjects experienced any significant undesirable side effects; specifically, no seizures were induced by rTMS.

In a follow-up study (Fig. 6), we applied right or left prefrontal rTMS to patients with MDD (DSM IV and SCID) (Catalá et al., 1996; Tormos et al., 1996). The study was designed as a cross-over trial in which patients received daily rTMS sessions for 10 consecutive days followed by a 4-month follow-up period. Daily stimulation sessions consisted of 1,600 stimuli applied in trains of 2–8 s with at least 30-s intertrain intervals. Stimulation parameters varied across patients depending on the effects of different rTMS parameters on motor corticospinal excitability. In all patients, stimulation parameters were used that induced an increase in cortical excitability when applied to the motor cortex. In most cases, this resulted in stimulation parameters of 10–20 Hz and 80–100% of patient's motor threshold intensity. Left prefrontal rTMS resulted in significant decreases in HDRS and BQ scores in almost 70% of the patients and in some cases lasted as long as 6 months despite unchanged, minimal antidepressant medication. All patients tolerated the procedure without complications. In particular, no seizures were induced by rTMS except in 1 patient who started using tricyclic and neuroleptic medications against our advice and without communicating it to the investigators.

In a single case study, George et al. (1995) showed that clinical antidepressant response to daily rTMS applied to the left prefrontal cortex apparently is associated with increased brain metabolism on ¹⁸F-DG-PET scans. In our study, we also noted that a positive response to rTMS in depression appears to be associated with normalization of the left prefrontal dysfunction, as shown by SPECT and a global increase in CBF (Tormos et al., 1996). Therefore, neuroimaging data, although still preliminary, appear to support the notion that rTMS results in beneficial, antidepressant effects by normalizing the disturbed level of cortical excitability.

Other potential therapeutic applications of rTMS are being explored, based on the same principle of modulation of cortical excitability with rTMS. For example, patients with bradykinetic Parkinson's disease have a decreased level of activity in motor cortex and SMA and rTMS can enhance activity in these regions and decrease slowness of movement for days to weeks (Pascual-Leone et al., 1994b, 1995). On the other hand, low-frequency rTMS appears capable of normalizing abnormally enhanced motor cortical excitability in pa-

tients with dystonia and lead to a symptomatic improvement for hours to days (Siebner et al., 1998). Similar approaches might be used to study the effects of rTMS of the orbitofrontal cortex in obsessive compulsive disorder (Greenberg et al., 1997), of the supplementary motor cortex on tics, of the motor cortex on cortical myoclonus, or of a seizure focus on spike and seizure frequency in focal epilepsy. Even if the effects of rTMS prove to be too short-lived or too variable to have a therapeutic effect, the effects of medications might be enhanced by coupling them with rTMS.

The long duration of the symptomatic effects of rTMS in all these conditions raises further questions regarding the mechanisms of action: A sustained effect for weeks to months cannot be explained solely on the basis of modulatory effects of rTMS on cortical excitability. rTMS may exert effects not only on the cortical region directly targeted by the stimulation, but also may have more widespread effects on other cortical and subcortical structures transsynaptically. Studies combining rTMS with SPECT or PET support this notion (described herein). In addition to widespread effects on functional cortico-subcortical networks, rTMS may induce expression of early genes that may have a critical role in a cascade of events resulting in the sustained behavioral effects noted.

Finally, the potential of this modulatory effect of TMS on cortical excitability in acquisition of new skills or recovery of function after brain lesions could be explored. Could rTMS, by modulating cortical excitability, serve as a guide of neural plasticity to enhance it or suppress it for the best functional outcome in a given subject and circumstance? Again, much research is needed. However, a few examples support this hypothesis. Implicit procedural learning of a sequence of finger movements in the serial reaction time task is associated with enhancement of motor cortical excitability (Pascual-Leone et al., 1994a). In a recent study, Tarazona et al. (1997) showed that the degree of implicit learning is decreased after low-frequency rTMS and increased by higher frequency rTMS to the motor cortex. The parameters of rTMS used were shown respectively to decrease and increase motor cortical excitability in the subjects studied. Sham rTMS did not affect implicit learning, and real rTMS affected implicit learning independently of the effects on reaction and movement time. In another pertinent study, we used transient immobilization of a hand as an example of undesirable plasticity (Pascual-Leone et al., submitted). The nondominant hand of normal volunteers was immobilized for 5 days in a cast, resulting in a decrease in motor cortical excitability for the motor

cortical outputs to muscles of the immobilized hand that was coupled with a transient motor dysfunction after the immobilization. However, these changes were prevented by subthreshold high-frequency rTMS applied daily to the contralateral motor cortex at rTMS parameters that increased cortical excitability.

CONCLUSIONS

We have reviewed the ways in which TMS can be applied in a variety of paradigms to evaluate cortical excitability in neuropsychiatric disorders. These studies enhance our understanding of pathophysiology and may provide objective guides for neuropharmacology in the future. In addition to this "diagnostic" application, trains of rTMS may have a "therapeutic" role, particularly in MDD. The therapeutic potential of rTMS is based on the possibility of modulating cortical excitability for longer periods than the duration of the rTMS trains themselves. This modulation of excitability does not remain limited to the cortical area directly targeted by rTMS, but affects a wide distributed functional network through transsynaptic effects.

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