Enhancing Encoding of a Motor Memory in the Primary Motor Cortex By Cortical Stimulation

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Bütefisch, Cathrin M., Vikram Khurana, Leonid Kopylev, and Leonardo G. Cohen. Enhancing encoding of a motor memory in the primary motor cortex by cortical stimulation. J Neurophysiol 91: 2110 –2116, 2004. First published January 7, 2004; 10.1152/jn.01038.2003. Motor training results in encoding of motor memories, a form of use-dependent plasticity. Here we tested the hypothesis that transcranial magnetic stimulation (TMS) synchronously applied to a motor cortex engaged in a motor training task could enhance this plastic process. Healthy volunteers were studied in four sessions: training consisting of performance of directionally specific voluntary thumb movements (Train alone), training with TMS delivered during the execution of the training movement in a strictly temporal relationship to the motor cortex contralateral (Train + TMS synchronous contral.) and ipsilateral (Train + TMS synchronous ipsil.) to the training hand, and training with TMS delivered asynchronous to the training movement to the motor cortex contralateral to the training hand (Train + TMS asynchronous contral.). Train alone, Train + TMS synchronous contral. and Train + TMS asynchronous contral. but not Train + TMS synchronous ipsil. elicited a clear motor memory. The longevity of the encoded memory was significantly enhanced by Train + TMS synchronous contral. when compared with Train alone and Train + TMS asynchronous contral. Therefore use-dependent encoding of a motor memory can be enhanced by synchronous Hebbian stimulation of the motor cortex that drives the training task and reduced by stimulation of the homologous ipsilateral motor cortex, a result relevant for studies of cognitive and physical rehabilitation.

INTRODUCTION

Motor training leads to encoding of kinematic details of the practiced movements in the human motor cortex (Classen et al. 1998), a form of use-dependent plasticity (Bütefisch et al. 2000; Classen et al. 1998). The operating mechanisms include changes in the balance of excitation and inhibition within the hand motor representation (Bütefisch et al. 2000, 2002; Classen et al. 1998; Sawaki et al. 2001) that are influenced by N-methyl-D-aspartate (NMDA), muscarinic and alpha-adrenergic receptor function as well as GABAergic neurotransmission (Bütefisch et al. 2000, 2002; Sawaki et al. 2001). It has been proposed that the mechanisms underlying this form of plasticity share similarities with those involved in long-term potentiation (LTP) (Bliss and Lomo 1973; Bütefisch et al. 2000; Rioult-Pedotti et al. 1998).

Use-dependent plasticity plays an important role in motor learning and recovery of motor function after brain lesions (Nudo et al. 1996), such as in patients with multiple sclerosis and stroke (Liepert et al. 1998, 2000; Reddy et al. 2000). Enhancing use-dependent plasticity may result in improvements in the ability of the CNS to compensate for the loss of function (Bütefisch et al. 2002; Feeney et al. 1982). Transcranial magnetic stimulation (TMS) is a technique that allows noninvasive focal stimulation of the human brain (Hallett 2000) and that, in particular settings, can enhance cortical reorganization (Ziemann et al. 1998a) and information processing (Boroojerdi et al. 2001; Flitmann et al. 1998). Therefore one possible strategy to enhance use-dependent plasticity could be the synchronous application of TMS to the motor cortex engaged in performing the training motions, a paradigm reminiscent of in vitro experiments in which stimulation of cortical afferents was paired with depolarization of the synaptic target neuron in a specific temporal relationship (Baranyi and Szente 1987; Baranyi et al. 1991). In the current study, we hypothesized that TMS applied to a thumb motor representation at a time it is engaged in driving a training motion would facilitate encoding of a motor memory for the trained movements.

METHODS

Subjects

Six of 11 healthy, right-handed volunteers (4 of them men; mean age: 34.2 yr; range: 23–42 yr) fulfilled the inclusion criteria (see following text) and gave written informed consent and participated in the study under a protocol approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke.

Experimental protocol

Subjects, unaware of the experimental purpose of the study, participated in different sessions testing the effects of four different interventions on the ability of training to form an elementary motor memory.

Encoding of a motor memory

Subjects were seated in a chair firmly connected to a frame that kept the head steady and the stimulating coil in a constant position with respect to the head. Head and coil stability were monitored with a three-dimensional laser system as previously described (Bütefisch et al. 2000). Each subject’s right forearm was immobilized in a molded armrest with the four long fingers supported and the thumb freely
movable. Thumb movements were recorded with a two-dimensional accelerometer mounted on the proximal phalanx of the thumb (Clasen et al. 1998). The direction of the thumb movements was calculated from the first-peak acceleration vector.

TMS was delivered from a custom-built magnetoelectric stimulator (Cadwell Laboratories, Kennewick, WA) through a figure-eight-shaped magnetic coil (wing diameter: 7.0 cm). The coil was placed tangentially to the scalp and rotated 45° away from the midline. The current induced in the brain was, therefore directed approximately perpendicular to the central sulcus, which is the optimal condition for activating the corticospinal tract transsynaptically (Kaneko et al. 1996; Werhahn et al. 1994). Stimuli were delivered to the optimal scalp position for eliciting mild isolated thumb movements. In addition to TMS-evoked movement directions, we recorded motor potentials (MEP) evoked by TMS from extensor pollicis brevis (EPB), a hand muscle mediating thumb movements in extension, and from flexor pollicis brevis (FPB), a hand muscle mediating thumb movements in flexion. MEP recorded from the muscle that acted as agonist to the training motions (see following text) is described as MEP_agonist whereas that recorded from the muscle that acted as antagonist to the training movements is described as MEP_antagonist. Motor threshold (MT) was defined as the minimum TMS intensity that evoked an MEP of ≥50 µV in ≥5 of 10 trials in the target muscle (Rossini et al. 1994). MT was determined to the nearest 1% of maximum stimulator output in the resting EPB and FPB muscles. MEP amplitudes after the training were expressed relative to MEP amplitudes at baseline.

Initially, we determined the direction of TMS-evoked thumb movements by stimulating the optimal scalp position overlying the contralateral motor cortex (total of 60 stimuli) at 0.1 Hz, a rate that does not affect cortical excitability (Chen et al. 1997). Subjects occasionally realized that the thumb had moved but could not determine its direction. In these trials, the baseline direction was defined as the mean angle of TMS-evoked movements that fell in the predominant direction (Fig. 1).

After identifying the baseline TMS-evoked thumb-movement direction, subjects practiced voluntary brisk thumb movements in a direction opposite to baseline in six blocks of 5 min for a total of 30 min at 1 Hz. After every single training movement, the thumb returned to the original position by relaxation as confirmed by electromyography (EMG). Acceleration and EMG signals of 20 training movements recorded at random in each training block were sampled at 1 kHz (120 training movements total). Quality of the motor training, as defined by the accuracy and consistency of training movements, was monitored on-line by one investigator. If necessary, the subject was encouraged to perform better. Additionally, quality and consistency of training movements was measured off-line by calculating the angular difference between the voluntary thumb-movement training direction and the TMS-evoked thumb-movement direction at baseline, the dispersion of thumb movement training directions, and the magnitude of the first-peak acceleration of these movements. The measure for dispersion of thumb-movement direction is derived from the length of the mean of the individual vectors in the unit circle. In a unit circle, a mean vector of 1 means that the direction of the individual vectors was identical, while a mean vector close to 0 means maximal dispersion (Batschelet 1981). At the end of the 30-min training period, TMS-evoked thumb-movement directions were recorded for 30 min (post 1–post 3, see following text) in all conditions. Because testing post 3 in Train+TMS synchronous, revealed
asynchronous contra motor cortex asynchronous to the training movements (tract neurons (Day et al. 1987). TMS at subthreshold intensities used in movements at 1 Hz in the absence of TMS as previously described

In this session, subjects performed voluntary thumb movements at 1 Hz in the absence of TMS as previously described

Subjects performed voluntary thumb movements at 1 Hz as in Train alone. A single TMS pulse was applied at ~0.1 Hz to the ipsilateral motor cortex at 80% MT, synchronous with 1 of every 10 voluntary thumb movements, using a second figure-eight coil connected to a second stimulator (triggered by the EMG burst in the muscle, acting as training agonist, when it reached a predetermined threshold amplitude level, ~10–20% of the maximal amplitude of the EMG burst).

This intervention was identical to Train + TMS synchronous, except that TMS pulses were applied asynchronous in relation to the training movements. Specifically TMS pulses were delivered regularly at 0.1 Hz at random in reference to the movements that occurred at 1 Hz.

Inclusion criteria

Participating subjects fulfilled the following inclusion criteria: ability of TMS to elicit isolated thumb movements in the absence of movements of any other digits, wrist, or arm; consistent (reproducible) direction of TMS-evoked thumb movements in the baseline condition; and postraining TMS-evoked thumb-movement directions matching the training direction.

Statistical analysis

The proportion of TMS-evoked movements in TTZ before (baseline) and after (post 1 training) were compared using Wilcoxon signed-rank test. A distribution-free Friedman rank test compared changes in the proportion of TMS-evoked movements falling in the TTZ after the different interventions calculated for the entire 30-min postraining period (post 1-3 post). Wilcoxon signed-rank test was used to compare the magnitude of these changes for the entire 30-min postraining period of each intervention relative to Train alone and to compare the training kinematics of each intervention relative to Train alone.

RESULTS

Motor threshold, movement threshold, and the amplitudes of MEP, MEP training antagonist, and MEP training agonist prior to the training did not differ across conditions (Train alone, Train + TMS synchronous, Train + TMS asynchronous, or Train + TMS synchronous/). Similarly, training kinematics, including magnitude of the first-peak acceleration of training movements, dispersion of training movement directions, and angular difference between mean baseline and training angle, did not differ significantly across conditions (Wilcoxon signed-rank test: NS, Table 2).

Formation of a motor memory

Training alone or combined with TMS applied to the contralateral M1 either synchronous or asynchronous to the EMG
activity of the agonist muscle (Train+TMS synchronous_contra and Train+TMS asynchronous_contra) resulted in a significant increase in the proportion of TMS-evoked thumb movements in the TTZ 0–10 min after completion of the training (post1) in reference to baseline (Wilcoxon signed-rank test: Train alone, \( P = 0.05 \); Train+TMS synchronous_contra, \( P = 0.03 \); Train+TMS asynchronous_contra, \( P = 0.05 \); Fig. 2). TMS applied to the ipsilateral M1 (Train+TMS synchronous_gpi) blocked this effect (Wilcoxon signed-rank test: NS; Fig. 2).

At baseline, the amplitude of MEP training antagonist exceeded that of MEP training agonist (Table 1). Consistent with the kinematic data, Train alone and Train+TMS synchronous_contra resulted in a differential modulation of MEP amplitudes, whereby the MEP training agonist increased and MEP training antagonist remained either unchanged or decreased (Fig. 3, A and B). Also consistent with the kinematic data, Train+TMS synchronous_gpi did not result in such differential modulation (Fig. 3D). In Train+TMS asynchronous_contra, both MEP training antagonist and agonist increased although MEP training agonist still exceeds MEP training antagonist (Fig. 3C).

Longevity of the encoded motor memory

The longevity of changes in TMS-evoked movement directions differed according to the intervention [Friedman rank test (post 1–post 3 pooled): \( P < 0.001 \); Fig. 3]. The changes lasted longer in Train+TMS synchronous_contra (Fig. 3B) than in Train alone [Fig. 3A; Wilcoxon signed-rank test (post 1–post 3 pooled data): \( P < 0.001 \), which was similar to Train+TMS asynchronous_contra [Fig. 3C; Wilcoxon signed-rank test (post 1–post 3: NS)].

Changes in TMS-evoked movement directions lasted for \( \sim 20 \) min in Train alone (Fig. 3A) and Train+TMS asynchronous_contra (Fig. 3C). Train+TMS synchronous_contra led to a substantial enhancement of the effect to \( > 60 \) min (Fig. 3B). Consistent with the kinematic data, the differential regulation of MEP training agonist and MEP training antagonist amplitudes in Train alone and Train+TMS synchronous_contra was present for \( \geq 30 \) min (Fig. 3, A and B). Data from a representative subject are shown in Fig. 4.

D I S C U S S I O N

The main finding of this study was that TMS enhanced training-dependent encoding of an elementary motor memory when applied synchronously to the motor cortex engaged in generating the practice movements.

Motor training leads to encoding motor memories in the CNS (Shadmehr and Brashers-Krug 1997). Under our experimental conditions, training leaves a memory trace in the primary motor cortex that reflects the kinematic details of the practiced movements (Classen et al. 1998). Here, we investigated if it is possible to enhance this plastic process by synchronous stimulation to the motor cortex engaged in the training motions, a proposal consistent with the Hebbian principle that potentiation of synaptic efficacy (LTP) occurs when its pre- and postsynaptic elements are simultaneously active (Hebb 1949). When inputs converge onto a target neural structure in temporal synchrony, they can enhance cortical plasticity (Baranyi and Feher 1981; Baranyi and Szente 1987; Iriki et al. 1989). With these considerations in mind, we hypothesized that application of TMS, a technique that stimulates preferentially intracortical connections targeting pyramidal tract neurons (Rothwell 1997) at a time when the motor cortex is engaged in generating a training motion, should lead to an enhancement in this form of plasticity. Previous work demonstrated that TMS can increase the excitability of the primary motor cortex (Pascual-Leone et al. 1994b), enhance deafferentation-induced plasticity in humans (Ziemann et al. 1998), and induce LTP- and LTD-like changes in slice preparations of cortical tissue (Wang et al. 1996).

Subjects participated in four different sessions testing the effects of motor training alone and motor training accompanied by TMS applied in synchrony and out of synchrony with the training motions. Preceding training, measures of corticomotor neuronal excitability, including motor thresholds (Mavroudakis et al. 1994), movement thresholds, and MEP amplitudes (Amassian et al. 1987; Ridding and Rothwell 1997) in two muscle groups controlling thumb movements, were similar across conditions. Additionally, monitoring of motor training kinematics revealed that the magnitude of the first-peak acceleration of training movements, the dispersion of training movement directions, and the angular difference between mean baseline and training angles did not differ significantly across conditions. The mean peak acceleration of training motions in
Train/H11001 TMS synchronous contra was slightly larger than in Train alone, similar to Train/H11001 TMS asynchronous contra (Table 2). It is possible that subthreshold TMS application in combination with training led to larger movement amplitudes. If present, this effect was very small because TMS was applied in only 1 of 10 trials, and in those trials, it did not evoke muscle twitches. More importantly, prolongation of learning occurred in the Train/H11001 TMS synchronous contra but not in Train/H11001 TMS asynchronous contra despite comparable acceleration levels. Overall, these results document comparable baseline motor cortical excitability levels preceding training and comparable motor training kinematics across the four interventions.

FIG. 3. Longevity of changes in the proportion of TMS-evoked movement in the TTZ (right y axis) and MEP training agonist (▲) and antagonist (▼) muscles (left y axis) after Train alone (A), Train+TMS synchronous_contra (B), Train+TMS asynchronous_contra (C), and Train+TMS synchronous_ipsi (D). Note that changes in the proportion of TMS-evoked movement in the TTZ lasted for ~20 min with Train alone (A) and Train+TMS asynchronous_contra (C) but for >1 h with Train+TMS synchronous_contra (B).

FIG. 4. TMS-evoked movement directions displayed as circular histograms in a representative subject at baseline, post 1 and post 2. (see Fig. 1B for details). Mean training angle (arrow) and TTZ for all conditions are shown in A. In the Train alone (A) and Train+TMS asynchronous_contra (C) conditions, TMS-evoked movements at baseline were mainly in the extension/abduction (ext./abd.) direction (inset). At post 1, there was a substantial increase in the proportion of TMS-evoked movements in the TTZ (flex./add.). After ~10–20 min (post 2), most TMS-evoked movements returned to the baseline direction. Note that Train+TMS synchronous_contra (B) elicited a more prominent and longer lasting change and that Train+TMS synchronous_ipsi (D) blocked the training effects.
First, we evaluated the effects of the different interventions on the formation of a motor memory. TMS applied to the motor cortex involved in the training task enhanced this form of plasticity, whereas TMS applied to the motor cortex ipsilateral to the training hand reduced it. This latter finding is consistent with interhemispheric competition models of cortical sensory processing (Mesulam 1999). Each hand motor representation exerts inhibitory influences on the homonomous representation in the opposite hemisphere (Di Lazzaro et al. 1999; Ferbert et al. 1992; Gerloff et al. 1998; Murase et al. 2004; Werhahn et al. 2002). It has been proposed that balanced interhemispheric interactions are required for the generation of proper voluntary movements (Ferbert et al. 1992). It is then possible that stimulation of the motor cortex ipsilateral to the training hand resulted in enhanced inhibitory drive exerted over the hand motor representation engaged in the training task, leading to the observed attenuation of the training effects (see Fig. 3D), a finding reminiscent of the reported reduction in deafferentation-induced plasticity in one hemisphere by application of TMS to the other hemisphere (Ziemann et al. 1999a). This proposal is consistent with the reported modulation of corticomotor excitability (Schambra et al. 2003) and intracortical inhibitory circuits in one hemisphere by stimulation of homologous motor areas of the opposite hemisphere (Daskalakis et al. 2002; Schnitzler et al. 1996). Additionally, \textit{Train+TMS synchronous} resulted in cancellation of training effects on encoding of this memory trace, consistent with a similar decrease in MEP amplitudes in agonist and antagonist muscles. It is of note that this form of plasticity relies on differential changes in excitability in agonist and antagonist muscles (Büttetsch et al. 2000) that were cancelled by application of ipsilateral TMS.

On the other hand, we found that stimulation of the motor cortex engaged in the training task enhanced the training effects if applied in synchrony with the training motions. Intracortical microstimulation (ICMS) alone results in cortical reorganization in the somatosensory and motor cortices in the rat (Nudo et al. 1990; Recanzone et al. 1992; Spengler and Dinse 1994). In humans, TMS increases motor cortical excitability (Pascual-Leone et al. 1994b) and can also facilitate functions mediated by the stimulated cortical areas (Boroojerdi et al. 2001; Flitmann et al. 1998). Interestingly, the facilitatory influence of TMS on training effects was observed in our study when stimulation was applied in synchrony with the training motions. The mechanisms underlying this effect remain to be determined. However, it is conceivable that LTP-like processes, known to operate in the motor cortex in vivo (Rioult-Pedotti et al. 1998) and thought to influence this particular form of plasticity (Büttetsch et al. 2000), could be enhanced by such Hebbian paradigm as also proposed when synchronized tactile-stimulation strategies were applied in the somatosensory system (Dinse et al. 2003). The duration of this elementary motor memory (>60 min when training was combined with synchronous stimulation but only \textsim{}20 min when TMS application was asynchronous to the training motions) is consistent with this hypothesis.

Therefore we demonstrate for the first time that it is possible to enhance the effects of motor training and the duration of this memory trace by noninvasive cortical stimulation. This form of memory encoding may underlie the beneficial effect of preperformance practice (for example, in athletics or musical performance), and it may be a requirement for purposeful skill acquisition in intact humans and in the rehabilitation of persons with brain damage (Büttetsch et al. 1995). The results raise the exciting possibility that cortical stimulation combined with rehabilitative treatment could lead to more prominent behavioral gains than rehabilitative treatment alone in patients with cortical lesions like stroke.

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\section*{References}


