RAPID COMMUNICATION

Rapid Plasticity of Human Cortical Movement Representation Induced by Practice

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Classen, Joseph, Joachim Liepert, Steven P. Wise, Mark Hallett, and Leonardo G. Cohen. Rapid plasticity of human cortical movement representation induced by practice. J. Neurophysiol. 79: 1117±1123, 1998. The process of acquiring motor skills through the sustained performance of complex movements is associated with neural plasticity. However, it is unknown whether even simple movements, repeated over a short period of time, are effective in inducing cortical representational changes. Whether the motor cortex can retain specific kinematic aspects of a recently practiced movement is also unknown. We used focal transcranial magnetic stimulation (TMS) of the motor cortex to evoke isolated and directionally consistent thumb movements. Thumb movements then were practiced in a different direction. Subsequently, TMS came to evoke movements in or near the recently practiced direction for several minutes before returning to the original direction. To initiate a change of the TMS-evoked movement direction, 15 or 30 min of continuous training were required in most of the subjects and, on two occasions, as little as 5 or 10 min. Substantially smaller effects followed more direct stimulation of corticofugal axons with transcranial electrical stimulation, pointing to cortex as the site of plasticity. These findings suggest that the training rapidly, and transiently, established a change in the cortical network representing the thumb, which encoded kinematic details of the practiced movement. This phenomenon may be regarded as a short-term memory for movement and be the first step of skill acquisition.

INTRODUCTION

Sustained repetitive electrical stimulation of the motor cortex (Nudo et al. 1990) and extensive training to perform specific upper limb movements (Cohen et al. 1996; Elbert et al. 1995; Karni et al. 1995; Nudo et al. 1996; Pascual-Leone et al. 1994, 1995; Schlaug et al. 1994) results in reorganization of the forelimb cortical motor area in experimental animals and in humans. Motor plasticity also can occur in a much shorter time scale as demonstrated under a variety of experimental conditions (Brasil-Neto et al. 1993; Jacobs and Donoghue 1991; Sanes et al. 1992). It is, however, unclear whether reorganization in the motor cortex in the short term already can be triggered by a brief performance of movements. Although previous behavioral paradigms studied plasticity associated with intentional acquisition of motor skills, it is an open question whether repetitive performance of simple and unskilled movements can cause representational changes. Also, it is unclear whether the reorganized cortical motor representation can code specific kinematic aspects of training.

To address these questions, we examined whether the direction of transcranial magnetic stimulation (TMS)-evoked thumb movements can be modulated by repetition of simple thumb movements during a short period of time. TMS at weak stimulus intensities predominantly activates pyramidal tract cells indirectly via their afferent input (Rothwell et al. 1991) and thus reflects properties of the stimulated neuronal network. When delivered to the optimal scalp position for stimulation of the motor cortex (Cohen et al. 1990; Wassermann et al. 1996), TMS can elicit isolated and reproducible thumb movements in most individuals. The hypothesis of these experiments was that performance of simple, unskilled repetitive thumb movements can trigger plasticity and that these plastic changes encode kinematic details of the practiced movement.

METHODS

Procedure and subjects

Subjects were seated comfortably in a chair firmly connected to a custom-built aluminum frame designed to immobilize the head and keep the stimulation coil in a constant position with reference to the head. The subject’s right forearm was immobilized in a semipronated position in a molded arm rest. The thumb was left entirely free to move and the other fingers were supported at their base in a slightly extended position. Of 24 subjects, 20 of them (12 men and 8 women) aged 20±64 yr (mean 37.5 yr) fulfilled the inclusion criteria, which specified that only isolated thumb movements must be evoked by TMS (no movements of the long fingers or hand), and that thumb movements must be evoked in a consistent direction with stimulus intensities slightly above the movement threshold.

Some subjects were studied multiple times in different experimental sessions, with intersession intervals of ≥14 days. Data from five experimental sessions were excluded from the analysis because a stable head position could not be maintained (3 sessions), the subject fell asleep (1 session), or posttraining thumb movements were no longer isolated (1 session). All subjects were right-handed, according to the Oldfield handedness inventory (Oldfield 1971), had normal results on physical and neurological examinations, and gave their written informed consent. The protocol was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board.

Recording

Movements were recorded with two miniature high-output charge accelerometers (model 137, Wilcoxon Research, Rockville,
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Experimental design

The principal experiment was designed to determine whether training to move in a direction opposite that of TMS-evoked movements would result in a change in the direction of subsequent TMS-training to move in a direction opposite that of TMS-evoked movements. In one of the six direct experimental sessions, which were excluded from analysis. The minimal stimulus intensity capable of inducing consistent isolated thumb movements (105–113% of movement threshold) was used. Electrical brain stimulation (TES) was performed using a Digitimer D180 (maximum stimulator output 750 V, 1 A). The anode was placed 6 cm lateral to the cathode, which was placed on the vertex. Surface electromyographic activity (EMG) was recorded from the abductor pollicis brevis (APB) and flexor pollicis brevis (FPB) muscles. EMG signals were amplified using a Dantec Counterpoint electromyograph (Dantec, Medical A/S, Skovlund, Denmark) and band-pass filtered between 20 and 3,000 Hz. EMG and accelerometer signals were digitized at a frequency of 3 kHz using an A/D converter and a data collection program written in LabView (National Instruments, Austin, TX).

Stimulation

TMS was performed with the subject at complete rest (defined as absence of visible or audible background EMG activity exceeding the noise level of 25 μV) with a custom-built Cadwell magnetoelectric stimulator (Cadwell Laboratories, Kennewick, WA). An 8-shaped magnetic coil (diameter of each wing 4.5 cm) (Cohen et al. 1990) was used with the handle pointing backward and laterally at a 45° angle to the sagittal plane. The optimal scalp position for activation of APB was identified using a stimulus intensity sufficient to evoke small thumb movements and marked directly on the scalp with a soft-tip pen. The movement threshold was defined as an acceleration of ≥0.09 m/s² in one axis. Movement threshold was 55.2 ± 4.8% (mean ± SD) of the maximal stimulator output and, on average, 0.9% of the maximal stimulator output higher than the EMG threshold for activation of the APB muscle. Resting EMG threshold intensity for activation of APB was established as that which evoked a potential of ≥50 μV at a gain of 50 μV per division in 5 of 10 trials (Pascual-Leone et al. 1994). The subject’s head then was fixed to the aluminum frame by an adjustable plastic band around the forehead and occiput. The coil was mounted on the frame and repositioned to correspond with the marks on the scalp. Coil position was checked frequently and remained stable throughout the experiments except in three of the sessions, which were excluded from analysis. The minimal stimulus intensity capable of inducing consistent isolated thumb movements (105–113% of movement threshold) was used. Electrical brain stimulation (TES) was performed using a Digitimer D180 (maximum stimulator output 750 V, 1 A). The anode was placed 6 cm lateral to the cathode, which was placed on the vertex. Stimulus intensities were on average 61 ± 18% of maximal stimulator output using a stimulus width of 100 μs. TMS differs from TMS, because it activates a higher proportion of the output neurons directly at the axon, where excitability is largely independent from afferent input (Day et al. 1987; Rothwell et al. 1991).

Experimental design

The principal experiment was designed to determine whether training to move in a direction opposite that of TMS-evoked movements would result in a change in the direction of subsequent TMS-evoked movements. The directions of TMS-evoked and voluntary movements were estimated by the direction of vectors constructed from the first-peak acceleration in the two orthogonal axes of the principal movement plane (Fig. 1A). This plane was defined by the axes of abduction and adduction or flexion and extension with the resting position of the thumb at its center. Preliminary experiments using an optoelectronic system based on infrared light-emitting diodes confirmed, in agreement with theoretical considerations, that directions derived from first-peak acceleration corresponded with directions determined from displacement in the movement plane. In the present study, “direction” refers to the direction of the first-peak—acceleration vector.

A pretraining (“baseline”) direction of thumb movements was established by delivering 60 magnetic stimuli at 0.1 Hz to the scalp during 10 min while the hand remained at rest. EMG was monitored throughout the experiment, and trials showing background EMG activity (<5% of all trials) were excluded from analysis. The baseline direction of TMS-evoked thumb movements (e.g., a combination of extension and abduction) varied between subjects. Brisk voluntary “training” movements of the thumb were made for 30 min in a direction approximately opposite that of the baseline movements. For example, if the baseline TMS-evoked movements were in an extension and abduction direction, the subject was asked to move in the flexion and adduction direction. Training movements were paced by a metronome beat of 1 Hz and were visually monitored by the investigators. During training, the instructions were repeated frequently to ensure attention to the task. An average of 135 ± 31 movements, or approximately five per minute, were sampled in each subject during training.

After training, TMS was delivered for 40 min at the same rate and intensity as for the baseline movements. Several variations of the principal experiment (training directions other than 180° from baseline, different training durations, random training directions, isometric contraction, stimulation alone in the absence of training) were performed using TMS and are described in more detail in RESULTS. TES experiments were performed in six subjects. TES-evoked movement directions posttraining were compared with movement directions evoked before the training. In one of the six subjects, and in a second experimental session with one of the other five subjects, TES-evoked movement direction matched the TMS-evoked movement direction and TES and TMS stimulations were intermixed in the same experimental session.

RESULTS

Nine subjects participated in the principal experiment. After training of unidirectional, stereotyped thumb movements for 30 min, TMS-evoked movement vectors changed toward the direction of training (Fig. 1B). This change was present for ~15–20 min, before the movement vectors returned to nearly the original direction. Results from different subjects were compared by calculating angular deviations from the average of the pretraining vectors (“baseline vector”) for all individual trials, pretraining and postraining (Fig. 2, A and B, top). The training direction was obtained from the average of all training vectors and differed from the baseline by 162 ± 14°. Results were averaged during 5-min epochs and across subjects (Fig. 2B, bottom). A one-way analysis of variance performed on the binned data revealed a significant effect of time interval (F = 20.52, P < 0.001). The pretraining pair of 5-min epochs was compared with all posttraining pairs of neighboring 5-min epochs. Post-hoc paired t-tests revealed significant effects for the first four (0–20 min) postraining pairs of 5-min epochs (P < 0.01, Bonferroni-Dunn correction for multiple comparisons). Comparable results were obtained with circular paired comparisons (P < 0.01, Watson U² test) (Batschelet 1981). The experiments were repeated on two (1 subject) or three (2 subjects) different days and yielded similar results.

During the baseline period, TMS-evoked movements had a mean first-peak acceleration of 0.85 ± 0.62 m/s², as calculated by the length of the first-peak—acceleration vector. TMS evoked a motor evoked potential in the APB and FPB of ~20- to 30-ms duration. Training movements were sub-
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**Fig. 1.** A: principles of movement recording. Original acceleration signals in the horizontal (abduction and adduction) and vertical (extension and flexion) axes of thumb movements. Direction of transcranial magnetic stimulation (TMS)-evoked or voluntary movement was derived from the 1st-peak acceleration in the 2 major axes of the movement. B: directional change of 1st-peak-acceleration vector of movements evoked by TMS after 30 min training in a representative subject. Pretraining, TMS evoked extension and abduction thumb movements. Training consisted of repetitive stereotyped brisk thumb movements in a flexion and adduction direction. TMS-derived vectors are grouped into intervals of 5 min. For clarity, vectors representing only the last 3 min of training are shown for training movements. Posttraining, the direction of TMS-evoked thumb movements changed from the pretraining direction to the trained direction. Movement angle gradually changed back toward the pretraining direction after ~15–25 min. Calibration bars (right) refer to both the pre- and posttraining vectors.

Substantially more accelerated (1st-peak acceleration 9.09 ± 4.41 m/s²; c.f., Fig. 1B) than the TMS-evoked movements. Typically, the training movements were associated with a burst-like activity of APB or FPB lasting between 70 and 200 ms. Posttraining, TMS-evoked movements were slightly more accelerated (1.06 ± 0.79 m/s²) than before the training. This difference was statistically insignificant, when the means of the first-peak accelerations calculated during the baseline period were compared with the means of the first-peak acceleration posttraining (paired t-test). When statistical tests were performed on the data of individual subjects, significantly larger first-peak accelerations of TMS-evoked movements were found posttraining in four of the nine subjects (t-test; P < 0.05). Directional change of TMS-evoked movements in these four subjects (131 ± 24°) was slightly larger than the directional change in the remaining five subjects (113 ± 16°; NS, t-test).

In addition to training at 180°, some subjects made training movements ~90° (3 subjects) or 45° (1 subject) away from the pretraining (baseline) direction. Two subjects, who did not participate in the principal experiment, trained with a movement 90° from the baseline direction, and another subject was studied with 45, 90, and 180°. The posttraining directional change, as defined by averaging the first 10 min of posttraining angular deviations from the baseline vector, correlated significantly with the angular deviation of the trained direction from baseline vector (y = 0.750x − 1.392, r = 0.84, n = 13, P < 0.001; Fig. 2C).

Additional experiments were performed to investigate further the specificity of the training effect. TMS alone for 1 h (5 subjects), tonic isometric contraction (30 min at 10% of maximal voluntary force) opposite to the baseline direction (2 subjects), and training of random thumb movements (in 8 balanced directions; 4 subjects) did not produce a directional change in TMS-evoked movements (not illustrated).

To examine the influence of the training duration, several subjects performed unidirectional thumb movements at ~180° of the baseline direction for variable (5 min, 5 subjects; 10 min, 3 subjects; 15 min, 4 subjects) periods of time. Only 20 trials (equivalent to a time period spanning 3 min 10 s) immediately after training were compared with 20 trials immediately before training to account for the possibility that a training effect would last shorter with a training duration shorter than 30 min (t-test, significance level P < 0.05). Mean training angles were similar under all condi-
FIG. 2.  A: quantification of angular changes. Pretraining vectors were averaged (bold solid arrow) and the absolute angular deviation from the averaged vector was calculated for each individual trial (examples of single trials are shown with thin solid arrows). Training direction is indicated by the broken arrow. B: time course of the change in movement vector direction in 9 subjects whose training thumb movements were in approximately the opposite direction of the pretraining vector direction. Top: data points represent all single trials of the 9 subjects. Bottom: data were averaged during bins of 5 min and across subjects. Error bars represent standard errors. Posttraining, angular deviation from the baseline vector was significantly different from the pretraining pair of 5-min bins for the first 4 pairs of neighboring 5-min bins (0-20 min; P < 0.01). C: relationship between trained movement direction and posttraining TMS-evoked movement direction. Average of the first 10 min posttraining correlated linearly with the trained angle.

tions (5 min: 160°; 10 min: 159°; 15 min: 158°; 30 min: 162°). A shorter training duration led to a significant change in only one of five subjects after 5 min, one of three after 10 min, and two of four after 15 min of training (Fig. 3) while in all subjects a significant directional change was noted after 30-min training. One subject was tested multiple times for various training durations on different days. A significant directional change was produced in none of three different sessions with 5-min training duration, in one of two sessions of 15-min duration, and in three of three sessions with 30-min duration.

TES was tested in six subjects by delivering 15 electrical pulses to the scalp before and after 30 min of training thumb movements in the direction opposite that of the TES evoked movements. The posttraining angular deviation from the baseline direction was significantly smaller with TES (42 ± 40°, absolute values) than with TMS (120 ± 21°; Fig. 4A; P < 0.01; t-test).

Plasticity may be masked by background motor activity (Ridding and Rothwell 1995; Topka et al. 1991). Therefore, one could hypothesize that a subliminal excitation of the spinal motoneuron pool could have the same obscuring effect on cortical plasticity as overt muscle activation. A greater subliminal excitation likely would have led to a greater number of excluded trials with TES as compared with TMS. The percentage of excluded trails was slightly lower with TES (1.9%) than with TMS (4.1%). In two subjects, we could compare directly the effects of TES and TMS in the same experimental session. In those experimental sessions, TMS and TES evoked isolated thumb movements with similar baseline directions. TMS and TES were delivered either in subsequent blocks (subject 1, Fig. 4B) or randomly, and
evidence supports the view that the earliest signal emanating from the motor cortex, relative to movement or force onset, represents the initial direction of movement, with amplitude and other information developing later (Fu et al. 1995). Together, these data suggest a dominant representation of initial movement direction in motor cortex, corresponding in the present paradigm to the direction of the first-peak acceleration vector, and it is likely that this parameter was most significant for producing the training effect described here.

In theory, plasticity of movement representation induced by training could have occurred at a cortical level or at a spinal level or both. The spinal neuronal circuitry has been shown to exhibit adaptive plasticity in experimental animals (Wolpaw and Carp 1993) and in humans (Baylor and Benjuya 1989). Because TES produces a greater proportion of direct activation of corticospinal neurons than TMS (Day et al. 1987; Rothwell 1997; Rothwell et al. 1991), movements unpredictably intermixed (subject 2, Fig. 4B). Posttraining, TMS-evoked movement direction matched the training direction whereas TES-evoked movement direction did not (Fig. 4B).

**DISCUSSION**

Brief performance of simple voluntary thumb movements results in a transient change in the direction of thumb movements evoked by TMS, toward the training direction. This finding indicates that a reorganization of the neuronal network mediating thumb movements takes place with the simplest repetitive movement and that it encodes, in the short term, certain kinematic aspects of the practiced action.

What kinematic aspects of the training movements altered the TMS-evoked movement direction? One possibility is that the TMS-evoked movement was a replicate of the training movement in all kinematic details. However, our findings show that the training movements need not be identical to the TMS-evoked movement in parameters other than direction, e.g., they are dramatically different in terms of peak acceleration amplitude and movement duration. Thus we suggest that the most important parameter of the training was the initial direction of force or movement. This conjecture seems likely because force or movement direction is the motor parameter most prominently represented in motor cortex. There is, of course, evidence for coding of movement or force amplitude (Fu et al. 1995; Maier et al. 1993; Taira et al. 1996) or speed (Schwartz 1994) in motor cortex. However, by far the majority of variance in motor cortical activity reflects the initial direction of movement (Schwartz 1994) or force (Taira et al. 1996). Experiments designed to differentiate between coding of force direction and coding of force amplitude have provided little evidence for a separate cortical representation of these two aspects of motor output (Taira et al. 1996), as have comparisons of movements versus isometric force pulses (Georgopoulos et al. 1992; Taira et al. 1996). Furthermore, recent neurophysiological
induced by TES should be less affected by training if this form of plasticity is mediated at cortical level. Our results indicate that the directional change of TES-evoked movements was substantially smaller than the directional change of TMS-evoked movements. Therefore the site where this form of plasticity takes place is more likely to be cortical than subcortical.

Movements result from a synergistic action of motor outputs, which are interconnected (Keller 1993) by inhibitory and excitatory pathways. The balance of these connections is likely to govern the kinematics of voluntary movements and also of movements induced by cortical stimulation. This pattern of connectional weights is regulated by mechanisms that alter the efficacy of synapses (Donoghue et al. 1996; Markram and Tsodyks 1996), and the neocortex is richly equipped with mechanisms for changing synaptic efficacies (Donoghue 1995). Of these, short-term potentiation or short-term depression are mechanisms possibly related to the present results. Short-term potentiation has been shown to be induced in the motor cortex of cats by paired stimulation of pyramidal tract neurons and afferent somatosensory pathways (Baranyi and Feher 1981).

The sort of plasticity described in this study may underlie the initial stages in acquisition of motor skills, a type of procedural memory, as well as in the recovery of function that follows rehabilitation from cortical injury. We propose that the capacity of the motor cortex to store kinematic information in the short term may be important in longer-term procedural learning, which is thought to involve both the basal ganglia (Graybiel 1995) and the cerebellum (Pascual-Leone et al. 1993) as well as cortical networks. On this view, our results may represent a short-term memory for a recently practiced movement. By analogy with the declarative memory system (Schacter and Tulving 1994; Squire 1994), we hypothesize that the storage and rehearsal of procedural information in short-term memory promotes the formation and consolidation of information in the longer term. This view is consistent with previous studies suggesting that the primary motor cortex is involved in the acquisition of procedural knowledge (Karni et al. 1995; Pascual-Leone et al. 1994).

From the present results, it appears likely that the motor cortex undergoes continuous plastic modifications. Frequently repeated movements reinforce particular network connectional patterns, but those patterns weaken if the movements have not been recently executed. This principle may underlie the beneficial effect of preperformance practice (e.g., in athletics or musical performance). It also may be a requirement for purposeful skill acquisition in intact humans and in the rehabilitation of persons with brain damage (Bütefisch et al. 1995).

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