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RESEARCH ARTICLE

J. Liepert · C.Terborg · C. Weiller

Motor plasticity induced by synchronized thumb and foot movements

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Abstract We used focal transcranial magnetic stimulation to examine the effects of 120 synchronized thumb and foot movements on the motor output map of the right abductor pollicis brevis muscle (APB) (experiment 1). To evaluate the performance, the latencies between the onset of the electromyographic activity (EMG) of the two muscles were measured. As control, 120 asynchronous thumb and foot movements were performed (experiment 2). Exclusively in experiment 1, the center of gravity (CoG) of the output map moved medially in the direction of the foot representation area (mean 7 mm, $P<0.05$) and returned into its original location within 1 h. In experiment 2, the CoG remained unchanged (mean displacement, 0.68 mm into a lateral direction; not significant). The effect in experiment 1 was independent of an improvement in performance. We conclude that a short-lasting training of synchronous movements induces modulations of motor output maps which probably occur due to interactions between hand and foot representation areas in the motor cortex.

Key words Transcranial magnetic stimulation · Plasticity · Synchronization · Motor system · Human

Introduction

Plasticity in somatosensory and motor cortices are induced by use-dependent mechanisms. In animal experiments, expansions of cortical sensory maps have been described following extensive stimulation of restricted skin areas (Jenkins et al. 1990; Recanzone and Merzenich 1994). Nudo et al. (1996) found use-dependent alterations of movement representations in the primary motor cortex (M1) of squirrel monkeys. In humans, Pascual-Leone et al. (1993) reported, in a series of experiments with healthy sighted volunteers and blind Braille readers, that learning of a motor task or repetitive performance of a movement resulted in expansions of motor output areas determined by focal transcranial magnetic stimulation (Pascual-Leone et al. 1993, 1995a, 1995b). Using the same technique, it was shown that immobilization induced a decrease in the motor output map of the involved muscle (Liepert et al. 1995). Recently, Cohen et al. (1995) demonstrated rapid plastic changes following training that consisted of synchronous movements of ipsilateral thumb and shoulder muscles (Cohen et al. 1995, 1996). They described displacements of the center of gravity (CoG) of the thumb muscle output map into the direction of the shoulder muscle representation area. The CoG is defined by the distribution of amplitudes of motor evoked potentials within the output map. Its location is reproducible within a range of 2–3 mm (Miranda et al. 1997).

In this study, we used the paradigm of synchronized movements to test whether interactions of areas extending the border of a single limb representation occur and to study the time course of the plastic changes we observed.

J. Liepert (✉) · C.Terborg · C. Weiller
Neurologische Universitätsklinik, Friedrich-Schiller-University, Philosophenweg 3, D-07743 Jena, Germany
e-mail: liepert@neuro.uni-jena.de

Materials and methods

Transcranial magnetic stimulation (TMS) was applied using a figure-of-eight-coil that was attached to a Magstim 200 HP (Magstim, Dyfed, UK). This coil allows a focal stimulation of restricted brain areas and is widely used in mapping studies of the human motor cortex (Ferbert et al. 1992; Wilson et al. 1993; Liepert et al. 1995). The coil was positioned tangentially to the head in an anterior-posterior direction, with the grip pointing backwards. The hand representation area was mapped systematically by moving the coil in steps of 1 cm over the skull. For orientation, we identified Cz as the intersection of the interaural line and the nasion-inion connection. Then a coordinate system (1×1 cm width) was either marked on the skull of the volunteer or on a tightly fitting cap the volunteer was wearing. Thus it was possible to localize positions on the skull in relation to Cz. On each position, using TMS, eight stimulations were applied with an intensity of 110% of motor threshold. The motor threshold was defined as the minimum stimulator output intensity that produced

five motor evoked potentials (MEPs) of more than 50 μV in ten trials. The MEPs were recorded from the right abductor pollicis brevis muscle (APB) with surface electrodes. TMS was performed during complete muscle relaxation. A loudspeaker was connected to the EMG channel and made any muscle contraction audible.

We studied 13 healthy volunteers (mean age 26.6±5.7 years; 9 men, 4 women). The subjects were seated comfortably in an armchair. Their forearms rested on the arms of the chair, but their feet did not touch the ground.

In experiment 1, the subjects (n=9) had to perform 120 synchronized thumb abductions and foot extensions. The interval between the single trials was 20–25 s. The volunteers were encouraged to make brisk movements as synchronously as possible. Additional movements of proximal muscles of the upper or lower extremity or of trunk muscles had to be avoided. This was controlled by surface electrodes attached to abdominal and paraspinal muscles, and the deltoid and quadriceps muscle. The movements were self-initiated and stored on-line on an electromyograph (Viking IV; Nicolet). After each single trial, the interval between activation of the APB and the tibial anterior muscle (TA) was measured. The volunteer was informed about his or her performance and continuously encouraged to improve it. The training session lasted approximately 45 min.

In experiment 2, the same subjects (n=9) as in experiment 1 had to perform the same number and type of movement. This time, thumb and foot movements had to be asynchronous either with an interval of 2–4 s (n=6) or with an interval of exactly 2 s (n=3). The latter condition was chosen to control for attention. As the results in both subgroups were identical, they were summarized as one group.

In both experiments, the motor output area of the APB was mapped before and immediately after completion of the training. Each mapping procedure had a duration of 20–25 min.

In experiment 3, the time course was studied using four subjects, who performed the same movements as in experiment 1. The motor output area of APB was mapped before, immediately after, and 1 h after completion of the training.

The following criteria were used for analysis:

1. Motor thresholds before and after training.
2. Mean motor output areas. The size of the area was defined by the number of scalp positions whose stimulation evoked MEPs in the APB muscle (”active” positions). The mean motor output area was the number of active scalp positions of all volunteers divided by the number of volunteers.
3. Mean MEP amplitudes. First, the mean MEP amplitude for a single scalp position was calculated, then the amplitudes of all active scalp positions were summed up and divided by the number of active positions. Finally the mean of all subjects was calculated.
4. Centers of gravity. Each scalp position was defined as an x-y coordinate. The CoG is a single x-y coordinate, derived from the distribution of MEP amplitudes within the motor output area, and can be calculated. The formula is:

$$\left[\frac{\sum(x^{*}z)}{\sum z}\right]$$

with x as a position along the x-axis, expressed in centimeters in relation to Cz, and z as the amplitude.

The calculation of the CoG position for the y-coordinate is performed by substituting x- by y-values in the formula. Using this formula, events in the brain can be localized with a greater degree of precision than is possible by the TMS mapping itself, assuming that any underlying effect can be described by a unimodal spatial distribution.

The same subjects participated in experiment 1 and experiment 2. Therefore, the analysis of the pretraining CoGs in both experiments allowed us to study the reproducibility of CoG location. We kept an interval of 4 weeks between the two experiments. The order of experiments was mixed pseudorandomly across the subjects.

5. Intervals between the activation of the two muscles in experiment 1 were measured, and the mean intervals of trials 1–30 and 91–120 were compared to study the improvement of performance.
6. A correlation between the individual amount of improvement of performance (measured in milliseconds) with the individual extent of displacement of the CoG (measured in millimeters) was carried out.

For statistics an ANOVA for repeated measurements was calculated. Paired t-tests were used to compare pre- and post-training results. The level of significance was assumed at 5%.

Results

Motor thresholds

In both experiments, the motor thresholds were slightly lower after training (Table 1). The difference was not significant when comparing pre- and post-training and experiment 1 with experiment 2.

Area sizes

In both experiments, the mean area size of the APB output map was larger after training (Table 1). The difference was not significant when comparing pre- and post-training within one experiment or when comparing experiment 1 with experiment 2.

Mean MEP amplitudes

The mean MEP amplitudes increased in both experiments (Table 1). The differences were not significant when comparing experiment 1 with experiment 2 nor when comparing pre- and post-training within each experiment.

Table 1 Motor thresholds, expressed as a percentage of the maximum stimulator output intensity, mean area size, expressed as the mean number of active scalp positions, and mean motor evoked potential (*MEP*) amplitudes

	Experiment 1		Experiment 2	
	Before training	After training	Before training	After training
Motor thresholds (%)	38.9±8.9	38.1±8.8	40.0±10.7	39.9±10.5
Mean area size (n)	18.9±3.8	19.3±3.7	16.1±4.4	18.4±5.0
Mean MEP amplitudes (mV)	0.128±0.064	0.146±0.071	0.111±0.066	0.138±0.098

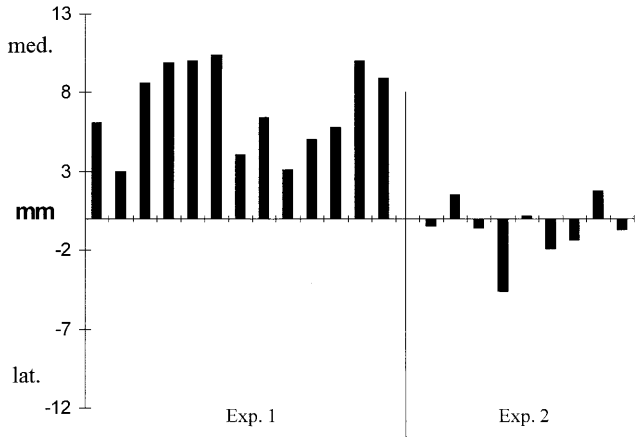

Fig. 1 Displacements of center of gravity (CoG) in experiment 1 and experiment 2. Each *bar* represents one subject. *Bars* on the *x*-axis that *point upward* indicate a displacement of the CoG medially, *bars pointing downward* show a displacement laterally

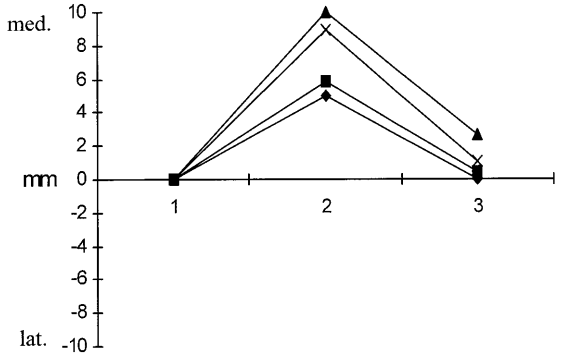

Fig. 2 Displacements of CoG in four subjects at different times. Position *1*,before the training; position *2*, immediately after completion of the training; position *3*, 1 h after completion of the training

Centers of gravity

The reproducibility after 4 weeks was as follows: a mean difference of 1.93 mm in the mediolateral direction (range 0.41–3.92 mm, $P>0.1$) and of 2.56 mm in the anterior-posterior direction (range 0.63–4.84 mm, $P>0.1$) was found in nine subjects.

In experiment 1, the CoG moved into a medial direction (mean 7.03±2.74 mm, $P<0.001$; Fig. 1). This effect was almost completely reversed 1 h after the training (experiment 3; Fig. 2). A displacement in anterior-posterior direction was not observed (mean 0.5±2.1 mm).

In experiment 2, the CoG remained basically unchanged (mean displacement 0.68 mm±1.9 mm into a *lateral* direction, $P>0.1$), although a few individual differences could be observed (Fig. 1). Again, no displacement in the anterior-posterior direction was seen (mean 0.85±2.3 mm).

Performance

In experiment 1, the mean interval between activation of APB and TA muscle was 22.5±11.4 ms when considering the first 30 trials. In trials 91–120, the mean interval was reduced to 17.8±10.3 ms, thus showing a mean improvement in movement synchronization of 4.7±7.5 ms. This was not significant. When analyzing single subjects, five subjects were able to improve their performance and four volunteers showed a small decrease in synchronization during the last quarter of the trials compared with the first 30 trials. There was no correlation between the degree of increased synchronicity and the displacement of the CoG ($r=0.105$, $P>0.1$).

Discussion

The main finding of this study is that synchronized thumb and foot movements induce a displacement of the CoG of the APB muscle motor output map toward the leg representation. The mean displacement of the CoG in experiment 1 exceeds by far the variability of CoG, owing to methodology. As the observed effect developed within 45 min and was reversed after 1 h, a change of excitability of preexisting synaptic pathways is much more likely than the development of new anatomical connections.

Shifts of representation areas were also observed in the somatosensory system of animals. Godde et al. (1996) applied paired tactile stimuli at different areas of the rat hindpaw that induced an increase and overlap of formerly distinct areas in the somatosensory cortex. Moreover, Clark et al. (1988) reported that surgical fusion of adjacent digits, leading to an increase in the amount of synchronized stimuli, resulted in a change of representation in the somatosensory cortex: areas formerly only responsive to the stimulation of a specific digit now responded to both of the fused digits, indicating that a cortical fusion of representation had occurred, too. Recently, a similar effect was observed in humans. Using magnetencephalography, a fusion of dipole localizations of the index and the third finger in healthy subjects who had a syndactyly of these two fingers for 3 weeks was described (Ziemus et al. 1997). In terms of the motor systems, our results point into the same direction as data presented by Cohen et al (1995), who found a displacement of the CoG of the APB representation area in the direction of the shoulder muscle motor output area after synchronized movements of APB and deltoid muscle.

The effects of synchronization or pairing of impulses are probably mediated by increasing the excitability of specific neuronal populations and by strengthening the efficiency of their synaptic pathways. The underlying principle could be the one presented by Hebb. He suggested that individual neurons could participate in different cell assemblies and be involved in multiple functions and representations (Hebb 1949; Nicolelis et al. 1997). This hypothesis was recently supported by Sanes et al.

(1995), who used functional magnetic resonance imaging to demonstrate that finger and wrist movements induced multiple sites of activation and had overlapping representations in M1. Georgopoulos et al. (1986) provided further evidence by describing neuronal populations that coded for different movement directions. Therefore, it is reasonable to assume that a preferential dynamic and task-dependent activation of specific motor areas within a broader and widely overlapping representation occurs. Additionally, horizontal connections probably contribute to the size and location of a cortical representation area. It was demonstrated that a loss of GABA-induced inhibition resulted in an expansion of the area size (Jacobs and Donoghue 1991) and that horizontal pathways are involved in synaptic plasticity by expression of long-term potentiation and long-term depression (Hess and Donoghue 1996). The most interesting finding in our study is that such plastic changes occur not only within a limb but also across the borders of a limb representation. We conclude that the synchronization of thumb and foot movements most probably increases the excitability of a specific subgroup of neurons coding for thumb movements by interactions between thumb and foot representation areas.

Does the displacement of the CoG depend on the improvement of performance? We did not find a statistically significant correlation between these two parameters. This might indicate that, in this paradigm, repetition of a movement is more important than the improvement of the motor performance. On the other hand, it may be that even the longest interval between thumb and foot movements (mean of 48.3 ms) is still effective in inducing plastic changes and that there is no need for improvement of performance. This assumption is supported by Baranyi et al. (1991), who found that pairing of pre-and postsynaptic activation with intervals of up to 200 ms still produced synaptic plasticity. Delacour et al. (1987) demonstrated plastic changes when pairing the stimulation of two whiskers in the awake rat. These changes occurred after 30–100 pairings with an interval of 500 ms between the first and the second stimulus. Therefore, even intervals longer than in our study might be sufficient to induce plastic changes. On the other hand, intervals of 2000 ms or more were unable to produce a similar effect.

Which is the anatomical substrate responsible for the observed changes? We used a low stimulus intensity for transcranial magnetic stimulation in order to avoid penetration of the induced current into subcortical areas. In addition, the way the coil was held induced an anterior-posterior flow of current that is supposed to stimulate pyramidal tract neurons transsynaptically (Werhahn et al. 1994). Therefore, it is highly probable that the effects induced by the training occurred on a cortical level, but additional subcortical changes cannot be excluded. To our knowledge, anatomical connections between cortical areas representing upper and lower extremities have not been described. Some indirect evidence of the existence of these connections was published by Brown et al. (1991). In patients with generalized cortical myoclonus, neuronal activity spread from hand to leg areas of the sensorimotor cortex within 10 ms, which might serve as indirect evidence of the presence of corticocortical connections between these two areas. This might indicate that, in normal subjects, preexisting connections between the two areas are inhibited. Training might reduce the extent of this inhibition. However, we cannot exclude that the neuroanatomical connectivity in these patients was completely different from controls. Outside M1, in the unimodal association cortex, the separation of limb representations is much smaller. In a recent study, Fink et al. (1997) found that in premotor areas and parietal inferior areas the coordinates for finger and leg movements were almost identical. It is possible that interactions induced by synchronous movements occur in these nonprimary motor areas. Changes of neuronal excitability and synaptic efficiency in the nonprimary areas might induce parallel changes in M1 owing to the multiple connections between these two areas.

Interactions between the areas of hand and face motor representation have been described by different groups: Rijntjes et al. (1997) reported enlargements and lateralizations of hand representation areas in patients with facial palsy; Liepert et al. (1996) found reversible reductions of hand representation area sizes in patients with hemifacial spasm; Birbaumer et al. (1997) demonstrated that in patients with an upper limb amputation the face representation is shifted into a medial direction; and Cohen et al. (1996) showed that synchronized movements of face and thumb induced a shift of the thumb representation area into a lateral direction. These studies indicate that interactions between anatomically distinct areas do occur and that the borders of cortical limb representations are much less tight than formerly believed.

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