RESEARCH ARTICLE

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Extensive training of elementary finger tapping movements changes the pattern of motor cortex excitability

Abstract There is evidence of a strong capacity for functional and structural reorganization in the human motor system. However, past research has focused mainly on complex movement sequences over rather short training durations. In this study we investigated changes in corticospinal excitability associated with longer training of elementary, maximum-speed tapping movements. All participating subjects were consistent right-handers and were trained using either the right (experiment 1) or the left thumb (experiment 2). Transcranial magnetic stimulation was applied to obtain motor evoked potentials (MEPs) from the abductor pollicis brevis (APB) muscle of the right and the left hand before and after training. As a result of training, a significant increase was observed in tapping speed accompanied by increased MEPs, recorded from the trained APB muscle, following contralateral M1 stimulation. In the case of subdominant-hand training we additionally demonstrate increased MEP amplitudes evoked at the right APB (untrained hand) in the first training week. Enhanced corticospinal excitability associated with practice of elementary movements may constitute a necessary precursor for inducing plastic changes within the motor system. The involvement of the ipsilateral left M1 likely reflects the predominant role of the left M1 in the general control (modification) of simple motor parameters in right-handed subjects.

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Introduction

Reorganizational changes in the central nervous system are thought to support learning processes. Use-dependent plasticity within the primary motor cortex (M1) through practice of voluntary movements is one such example (Amunts et al. 1997; Classen et al. 1998; Hazeltine et al. 1997; Karni et al. 1995; Muellbacher et al. 2001). Movement repetition, as one aspect of motor practice, has been intensively investigated in earlier studies where the focus was on complex (mostly sequential) movements. Training durations varied greatly, ranging from minutes to weeks. The within-session effects of movement repetition in previous studies do not provide consistent results for the accompanying neural activation, showing either decreases (Karni et al. 1995, 1998) or increases (Grafton et al. 1992; Iacoboni et al. 1996; Shadmehr and Holcomb 1997). In contrast, consistency has been reported in the slowly developing increase of activation (several days up to weeks) (Hlustik et al. 2004; Karni et al. 1995; Ungerleider et al. 2002). Transcranial magnetic stimulation (TMS)-based studies have addressed the issue of motor training and results suggest expansion and increased excitability of the neural representation of specific muscles involved in the training task (Classen et al. 1998, 1999; Cohen et al. 1993, 1998; Pascual-Leone et al. 1994, 2005). In addition to the application of diverse training paradigms in studies using untrained subjects, the investigation of skilled subjects

has received much attention, professional musicians being of chief interest (Munte et al. 2002) because they represent an adequate model of neuroplasticity. Skilled compared to non-skilled subjects show reduced neural activation in primary and secondary motor areas when performing the same motor action (Haslinger et al. 2004; Jäncke et al. 2000b; Koeneke et al. 2004; Lotze et al. 2003)—an effect that has been explained as reflecting the diminished neural effort required for a particular motor performance with a history of life-long, intense motor training.

Considerably less data are available on motor learning of more elementary movements, such as finger flexion/extension. Those movements belong to the motor repertoire all but since birth; they are frequently performed throughout life and form the basis of more complex, purposeful motor acts. While many studies have examined changes in neural activation accompanying the stereotyped repetition of elementary movements (Carey et al. 2000; Dejardin et al. 1998; Loubinoux et al. 2001; Morgen et al. 2004; Rajah et al. 1998; Tracy et al. 2001; Yetkin et al. 1996), only very few have explicitly investigated effects of training in terms of modifying single movement parameters like direction, acceleration or speed. Classen et al. (1998) have elegantly shown that the stereotyped repetition of a simple finger movement results in strong plasticity effects within M1. Their results clearly suggest the establishment of a memory trace with which kinematic details of the practiced movement are encoded (Classen et al. 1998, 1999). Training durations in studies on exercising elementary movements are generally in the range of several minutes. Thus, there is some need to study the neural activation changes associated with longer-lasting motor trainings.

A further interesting question is whether the contra- and ipsilateral motor cortices are similarly or differently involved in the process of motor learning—especially in the case of subdominant-hand training. Previous studies have uncovered several factors (e.g. hand dominance, task difficulty and effort) which determine the involvement of the ipsilateral hemisphere in the neural control of unimanual movements (Baraldi et al. 1999; Caramia et al. 2000; Chen et al. 1997a, b; Kawashima et al. 1993; Kim et al. 1993; Kobayashi et al. 2003; Verstynen et al. 2005). There have however been very few investigations of asymmetrical hemispheric involvement in motor learning to date. Some studies suggest that the dominant motor cortex is involved in learning with the right *and* left hand, while the subdominant motor cortex is only active during learning with the subdominant hand, asymmetrical transfer of information via the corpus callosum being the result (Halsband 1992; Schulze et al. 2002).

To address the issue of elementary finger movements and training-related changes in M1, we assessed corticospinal excitability using TMS before and after training aimed at increasing maximum thumb tapping speed. Since previous studies have shown that sequential movements rely on activations in a distributed neural network (Catalan et al. 1998; Harrington et al. 2000; Haslinger et al. 2002; Jäncke et al. 2000a; Sadato et al. 1996), we decided to use simple finger tapping training to avoid confounding influences from the entire motor system onto M1/S1. In addition, the present study aimed to improve our understanding of the role of the ipsilateral hemisphere during motor training of the subdominant hand.

Materials and methods

The current study consists of two experiments, both of which were designed to determine corticospinal excitability before and after motor training of elementary, repetitive thumb movements. Experiment 1 focused on motor training involving the right thumb (dominant hand) while experiment 2 investigated effects occurring during left-thumb training (subdominant hand). Data for both experiments were acquired over a period of about 2 years. Due to technical constraints we used a different stimulation device in experiment 2 (see below). In addition to this, we introduced two further measurement time points in experiment 2 to delineate the learning-related time course more precisely. However, since the electrophysiological data resulting from the two experiments were not directly compared, it is unlikely that the methodological differences put any substantial limitations on the interpretation of the data.

Subjects

Seventeen subjects took part in the two experiments (experiment 1—ten subjects/nine women, mean age 28.0 ± 2.9 years; experiment 2—seven subjects/four women, mean age 27.7 ± 1.1 years). Handedness was assessed with the Annett Handedness Questionnaire (Annett 1970) and the Hand Dominance Test (Jäncke 1996; Steingruber 1971). According to these tests, all subjects were classified as consistent right-handed subjects. None of the subjects showed signs of neurological or psychiatric disorders according to standard medical interviews. The study was approved by the local ethics committee. Each individual gave written informed consent. Tasks and testing procedures were in accordance with institutional guidelines and the study conforms to the Declaration of Helsinki (the code of ethics of the world medical association).

Transcranial magnetic stimulation

Magnetic stimulation was delivered with commercially available stimulators with biphasic waveforms (experiment 1—*MagLite-r25 with TwinTop Option, Dantec Medical, Skovelunde, Denmark*/experiment 2—*Magstim 220, Whitland, Dyfed, UK*) through figure of eight-shaped coils (experiment 1—*MCB70*/experiment 2—*Magstim Double 70 mm Coil*) that were placed tangentially to the scalp, with the handle pointing backwards and rotated away from the midline by 45°. This ensures

that the first quarter-cycle of the cosine waveform of the current induced in the brain is directed in a posterior-to-anterior direction, while the biologically more effective following half-cycle is directed in the opposite direction.

The TMS procedure for every muscle recorded at any time point of measurement was strictly uniform. First, focal TMS was applied to the contralateral hand area of the motor cortex in order to determine the optimal scalp position for consistently eliciting motor evoked potentials (MEPs) of maximal amplitude in the target muscle. This position was marked on the scalp with a pen to ensure an identical coil placement throughout the experiment.

The resting motor threshold (RMT) was then determined to the nearest 1% of maximum stimulator output in the resting target muscle while maintaining the coil at the optimal position. RMT was defined as the minimal stimulus intensity sufficient to elicit MEP greater than 50 µV base-to-peak amplitude in at least five out of ten trials (Rossini et al. 1994). Stimuli were delivered no more frequently than one every 10 s. The intensity of TMS pulses during the experimental sessions was adjusted to 120% of the RMT in experiment 1 and 110% of the RMT in experiment 2. A total of 20 MEPs per muscle were recorded to ensure collection of enough data to compensate for high variability, a known problem in recording cortically induced MEPs (Hess et al. 1987; Kiers et al. 1993).

Peripheral nerve stimulation

In order to control for changes of nerve and muscle excitability, maximal compound muscle action potentials (CMAPs) were determined by supramaximal electrical stimulation of the median nerve at the wrist for the left and right abductor pollicis brevis (APB) muscle, using a conventional electrical stimulator (*SIGMA Medizin-Technik GmbH, Germany*). Since we did not detect a significant change of the CMAP amplitude as a consequence of training in experiment 1, peripheral stimulation was no longer carried out in experiment 2.

Electromyography (EMG) recordings

Motor evoked potentials were recorded from the right and left APB using gold cup surface electrodes (11 mm diameter) filled with contact gel in a belly tendon montage. In experiment 1 MEPs from the right abductor digiti minimi (ADM) were additionally recorded in seven of ten subjects to test for the specificity of the training effect, since the ADM was not explicitly involved in training. To avoid high impedances, the skin was carefully prepared with cleaning pads soaked in alcohol and abrasive gel. The EMG signal was recorded with a conventional EMG electromyograph (*SIGMA Medizin-Technik GmbH, Germany*) using a bandpass of 20 Hz–3 kHz. The signal was digitized at a frequency of 50 kHz and stored on a personal computer for off-line analysis. Pulses were only applied in epochs without apparent baseline EMG activity.

Motor training

The motor training consisted of elementary, repetitive tapping movements performed with the right or left thumb (tapping on a key), strongly involving the APB muscle. In contrast to previous studies, we used training durations of several weeks (experiment 1—4 weeks/experiment 2—2 weeks of daily training; *for explanation, see below*). The subjects were given the aim of increasing maximum tapping speed. After the pretraining TMS session subjects were precisely instructed in how to carry out the motor training. They were told to put the right hand beneath the computer keyboard, with the thumb positioned on the *ENTER* key of the numeric keypad (*CTRL* key for training with the subdominant left thumb) and the remaining digits resting aside. Subjects were further advised to only involve the thumb during the tapping periods and to prevent the other digits from moving. One daily training session consisted of 30 consecutive trials that were made up of a movement execution period (20 s) and a resting period (40 s). The tapping training was carried out by the subjects on their home computers. In house software (*TapTrainer*) was used to guide the daily training sessions and to record particular training parameters, for example, inter-tap-intervals (ITIs) as indicators for tapping speed. This gave us the opportunity to track the course of training. We were therefore able to ensure that subjects accomplished the training regularly and in accordance with the instructions.

Experimental protocol

Experiment 1

Corticospinal as well as peripheral nerve excitability was determined before training (Exp1-T1) and after completion of the 4 weeks of training (Exp1-T2). For this, subjects were seated in a comfortable chair with forearms supported on a cushion and were instructed to keep their hands relaxed during the measurements. At the beginning of each measurement CMAPs were determined for the left and right APB. Afterwards MEPs were elicited from the target muscles (left and right APB, right ADM) in pseudo-randomized order. The motor training was carried out only with the right thumb (=dominant hand) and on a daily basis for an overall duration of *4 weeks* (1 day without training per week—resulting in a total of 24 training sessions).

Experiment 2

The experimental setup was the same as in experiment 1, with the exception that the left thumb now underwent motor training (=subdominant hand). In experiment 1, most pronounced increases in tapping speed were observed during the first training days. For experiment 2, we therefore decided to shorten the overall training duration to *2 weeks* (with 1 day without training per week—resulting in a total of 12 training sessions) and to focus on

the period of training where behaviour changes are greatest. In order to track modulations of corticospinal excitability in the left and right hemisphere in more detail, we recorded MEPs from the left and right APB at four time points: before training had started (Exp2-T1), 30 min after the first training session (Exp2-T2; both measurement and the first training took place in our laboratory), after 6 training sessions, that is, one training week (Exp2-T3), and after 12 training sessions, when training was fully completed (Exp2-T4). Based on the results of our first experiment, we abstained from peripheral stimulation and from additionally recording MEPs from the ADM muscle.

Statistical analysis

Data were analysed using standard parametric statistics. Given that all TMS and CMAP measurements were registered during complete muscular rest, we controlled whether or not subjects did profit from training and gained speed by analysing behavioural data recorded by the TapTrainer software (ITIs). For this purpose we calculated a mean ITI for each training session and further analysed these mean values using a repeated measures ANOVA with session number as within-subject factor. Due to recording problems of the TapTrainer software in two subjects in the second half of experiment 1, the ANOVA was calculated with 12 factor levels (=number of sessions) for both experiments. In experiment 1, only data of the first 12 training sessions were used. Increases of maximum tapping speed across the training were tested using trend analyses supported by SPSS software. Since statistics for multivariate tests cannot be calculated when there are more factor levels than subjects, Greenhouse–Geisser corrections for degrees of freedom were used to correct for possible violations of homoscedasticity (Keselman et al. 2001). In order to evaluate the training effect in experiment 1 over the whole training duration of 4 weeks, we determined mean ITIs for the beginning and for the end of training by averaging the recorded ITIs for the first three and for the last three training sessions for each individual separately. Additionally, changes in ITI variability were assessed by determining the averaged standard deviation of ITIs for the beginning and for the end of training. Mean ITIs and ITI variability for the two time points were compared using paired t-tests. To compare the magnitude of training effect between the two experiments we conducted a repeated measures ANOVA with 'time' (pre- vs. posttraining) as within-subject factor and 'study' (right-thumb vs. left-thumb training) as between-subject factor (involving the first 12 training sessions for both experiments).

Motor evoked potential amplitudes for each target muscle and time point of measurement were determined (by averaging peak-to-base amplitudes over 20 single trials) and subjected to a two-way repeated measures ANOVA with *time point of acquisition* (experiment 1—T1, T2/experiment 2—T1–T4) and *stimulated hemisphere* (left vs. right M1) as within-subject factors. Wilks Lambda was computed in the context of multivariate testing to conform to possible problems in homoscedasticity (O'Brien

and Kaiser 1985). Post hoc analyses were carried out using Bonferroni-corrected t-tests for paired samples, applying the correction procedure by Holm (1979).

Since P-values strongly depend on sample size we additionally calculated effect size measures to obtain information on how strong an effect is. ETA^2 (η^2) is reported in multivariate ANOVA statistics and describes the variance attributed to the independent variable of interest. For the t-tests, Cohen's d (Cohen 1988) was determined ($d = $ M1 - M2/σ_{pooled}), that is, the difference between two means divided by the pooled standard deviation. The pooled standard deviation is the square root of the average of the squared standard deviations (Rosnow and Rosenthal 1996). According to Cohen an effect size of $d > 0.5$ is considered as being moderate, while $d > 0.8$ is considered as being large (Cohen 1988).

Results

All subjects tolerated the single TMS pulses very well. Thus, there was no sign of discomfort and negative emotions, which might have influenced the results.

Experiment 1

One of the subjects was excluded from data analysis because of an injury sustained to the left wrist less than a year before study commencement. The injury might have altered corticospinal excitability and plasticity (Facchini et al. 2002; Zanette et al. 2004).

Behavioural results

Due to recording problems of the TapTrainer software in two subjects, the calculation of a repeated measure ANOVA for all subjects and training sessions was not possible. Instead, we determined mean ITIs for the beginning and for the end of training by averaging the recorded ITIs for the first three as well as for the last three training sessions for each individual separately. These mean ITIs underwent a paired t-test for nine subjects that revealed a significant decrease of the ITIs [T(8)=2.591, $P = 0.032$, one-tailed]. More detailed exploration of the data unveiled a marked increase of tapping speed at the end of training in only seven of the nine subjects. Since the focus of this study was to investigate changes of cortical plasticity resulting from behavioural training and because we were not sure about the reasons for this negative finding, we decided to exclude the two subjects who obviously did not profit from the training. Thus, as depicted in Fig. 1c, calculating the paired t-test for the remaining sample of seven subjects resulted in an even more significant effect of training [T(6)=3.41, $P < 0.01$, one-tailed, $d = 1.57$]. ITI variability did not change from pre- to posttraining measurements.

We additionally carried out a repeated measures ANOVA for seven subjects (showing a training effect)

Fig. 1 Inter-tap-intervals (ITIs) in milliseconds. *Left panel* Decrease of ITIs throughout the first 2 weeks of training for the left-thumb (*dashed line*) and for the right-thumb (*solid line*) training group (**a**). *Right panel* Averaged ITIs for the first three training sessions (=pretraining) and for the last three training sessions (=posttraining) separately for the left-thumb training group (**b**) and for the right-thumb training group considering the whole training duration of 4 weeks (**c**). Error information is given as SE
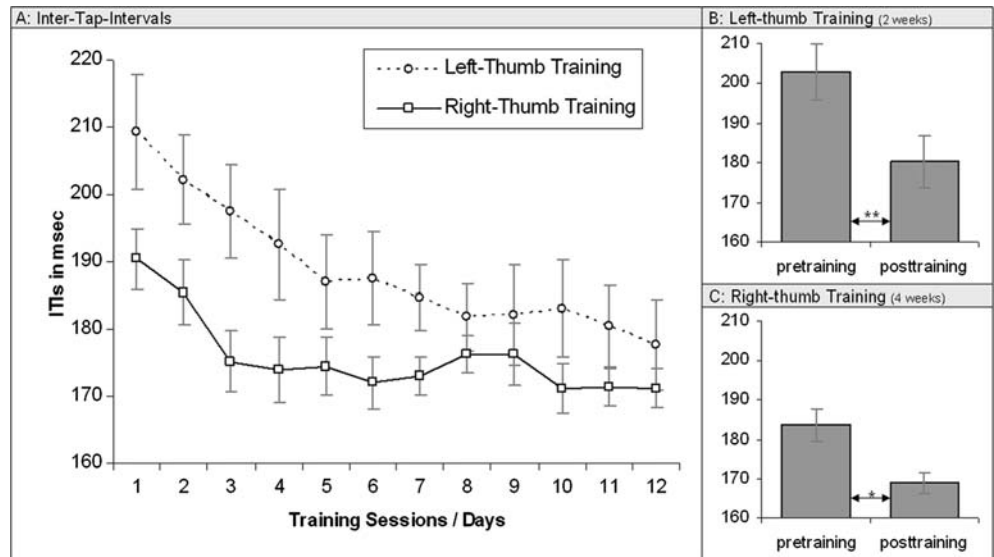
and the first 12 training sessions to make comparisons with the left-thumb training. The results of this ANOVA show a highly significant training effect [$F_{(3.3,19.5)}=5.517$, $P=0.006$, $\eta^2=0.48$]. Subsequently conducted trend analyses revealed a linear trend [$F_{(1,6)}=8.38$, $P=0.028$, $\eta^2=0.58$], a quadratic trend [$F_{(1,6)}=10.34$, $P=0.018$, $\eta^2=0.63$] and a cubic trend [$F_{(1,6)}=10.7$, $P=0.017$, $\eta^2=0.64$]. As can be seen in Fig. 1a, these trends are qualified by a strong decrease in ITIs during the first four training sessions followed by a period of less pronounced performance gains.

The description of further results of cortical and peripheral stimulation includes only the seven subjects showing a training effect in terms of faster tapping.

Compound muscle action potentials

In order to control for changes of nerve and muscle excitability, CMAPs were determined by supramaximal electrical stimulation of the median nerve at the wrist for the left and right APB. Comparing pre- and posttraining measurements by means of a *t*-test for paired samples, we did not observe a significant difference [mean CMAPs for the right APB—6.87±2.1 mV at T1 vs. 7.64±3.2 mV at T2/for the left APB—6.36± 1.79 mV at T1 vs. 6.60±1.5 mV at T2].

Resting motor threshold

Mean RMT was 33.3% (SD 5.7) of maximum stimulator output for the right APB, 32.9% (SD 6.3) for the left APB and 27.6% (SD 5.2) for the right ADM. The RMT did not change as a result of training (paired t-tests for all muscles, $P>0.1$).

Motor evoked potentials

The two-way repeated measures ANOVA (factor 1, right APB vs. left APB; factor 2, Exp1-T1 vs. Exp1-T2) revealed a significant interaction between the two factors

[$F_{(1,6)}=8.56$, $P=0.026$, $\eta^2=0.59$]. Subsequent post hoc *t*-tests for paired samples showed that this interaction effect was qualified by a *strong* increase of the MEP amplitudes recorded from the right APB at post- compared to pretraining measures [$T(6)=-2.31$, $P=0.060$, two-tailed, d=0.98, trend] (see Fig. 2). An increase of MEP amplitudes was not apparent for the left untrained APB muscle. Furthermore, MEP amplitudes evoked in the right ADM which was not involved in training and, thus served as another control, did not change during the course of training ($P>0.1$).

As suggested by previous studies (Rossini et al. 1994; Ziemann et al. 1998), we additionally calculated the relation of absolute MEP amplitude values to peripherally recorded CMAPs. Subjecting the *relative MEPs* to the same ANOVA model with *muscle* and *time* as within-subject factors resulted in a comparable interaction effect accompanied by a significant post hoc *t*-test [T1 < T2 (right APB)—T(6)=−2.77, $P=0.034$, two-tailed, d=1.27].

Experiment 2

Behavioural results

Analysing the mean ITIs obtained for each training session in the repeated measures ANOVA with 12 factor levels (=12 training days) revealed a highly significant training effect [$F_{(3.6,22.5)}=20.8$, $P<0.001$, $\eta^2=0.77$]. Subsequently conducted trend analyses revealed a strong linear trend [$F_{(1,6)}=76.0$, $P<0.001$, $\eta^2=0.93$] and a significant quadratic trend [$F_{(1,6)}=26.3$, $P=0.002$, $\eta^2=0.81$]. These trends are qualified by strongly decreasing ITIs during the course of training. As can be seen from Fig. 1a, the ITI decrease is steeper for the first 5 days, thus causing the quadratic trend. Comparison of the mean ITIs of the first and last three training sessions reveals a significant decrease of the ITIs after 2 weeks of training [T(6)=11.526, $P<0.01$, two-tailed, d=1.12]
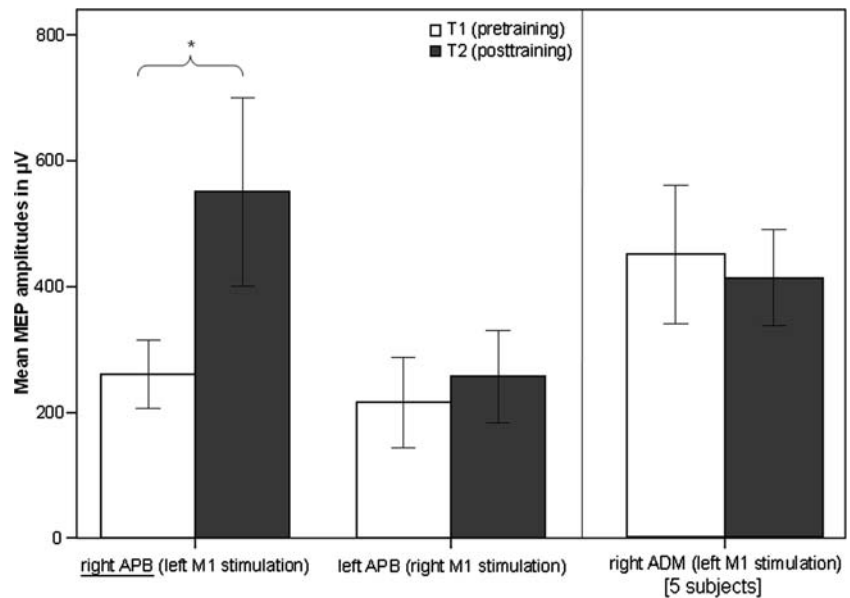
(see Fig. 1b). ITI variability decreased from pre- to posttraining measurements [$T(6) = 2.017$, $P = 0.045$, one-tailed]. Comparing the magnitude of training effect between experiments 1 and 2 (considering the first 12 training sessions of both studies) revealed a significant study × time interaction [$F(1,12) = 6.51$, $P = 0.025$, $\eta^2 = 0.35$] qualified by a significantly stronger training effect for the left compared to the right-thumb training.

Resting motor threshold

Mean RMT was 49.86% (SD 1.86) of maximum stimulator output for the right APB and 53.86% (SD 7.11) for the left APB. The RMT did not change as a result of training (paired t-tests for all muscles, $P > 0.1$).

Motor evoked potentials

The two-way repeated measures ANOVA (factor 1—right APB vs. left APB; factor 2—Exp2-T1 pretraining, Exp2-T2, Exp2-T3, Exp-T4 posttraining) revealed a significant interaction between the two factors [$F(3,4) = 6.54$, $P = 0.05$, $\eta^2 = 0.83$]. Mean MEP amplitudes for the left and right APB are displayed in Fig. 3. Inspection of the figure revealed a linear trend (increasing MEPs during the course of training) for the left APB. Formal testing by trend analysis revealed a significant positive linear trend [$F(1,6) = 9.58$, $P = 0.02$, $\eta^2 = 0.62$]. For the right APB (which was not explicitly trained) there was no significant linear trend but a tendency towards a quadratic trend [$F(1,6) = 3.2$, $P = 0.12$, $\eta^2 = 0.35$]. Closer examination of the data showed a strong trend for increased right-sided APB MEPs at Exp2-T3 [$T1 < T3$—$T(6) = -1.99$, $P = 0.94$, two-tailed, $d = 0.95$]. In addition, there was a large increase of MEP amplitude also at Exp2-T2; however, due to high variance this effect failed to reach the significance threshold [$T1 < T2$—$T(6) = -1.50$, $P = 0.18$, two-tailed, $d = 0.63$].

While the left M1 seems to be involved at the beginning of training, the right M1 shows a significant enhancement of MEP amplitudes only at Exp2-T3 and Exp2-T4, not immediately after the first training session [$T1 < T3$—$T(6) = -3.68$, $P = 0.01$, two-tailed, $d = 1.60$/ $T1 < T4$—$T(6) = -3.68$, $P = 0.008$, two-tailed, $d = 1.52$].

Discussion

The current set of experiments was designed to investigate changes in motor cortex excitability with concomitant intense, longer-lasting training of thumb tapping speed. Common to both experiments was the main finding of a pre- vs. posttraining increase in the mean MEP amplitude as recorded at the trained APB muscle, a result that indicates an increase in corticospinal excitability. Our data further indicate a differential involvement of the two hemispheres during subdominant-hand training, with the ipsilateral left M1 (dominant) playing a considerably greater role, particularly during the first training week.

Hand dominance determines the magnitude of speed increase

Comparisons of training effect size between the two experiments revealed a significant between-group difference qualified by larger speed gains in the left-thumb training group. These subjects were able to tap with the left thumb at the end of the 2-week training as fast as the right-thumb training group could with the right thumb prior to training. Given that experiment 2 was exclusively designed to examine the first 2 weeks of practice, providing greater time resolution, statements about further speed gains cannot be made with certainty. Even though the strongest decline of ITIs occurs during the

Fig. 3 Mean motor evoked potentials in microvolts and SEs recorded in experiment 2 (left-thumb training). T1—pretraining, T2—after the first training, T3—after the sixth training, T4—posttraining (after two training weeks). $^{\tau}P<0.1$ (trend)/ $*P<0.05$/$**P<0.01$. The muscle directly involved in training is *underlined*
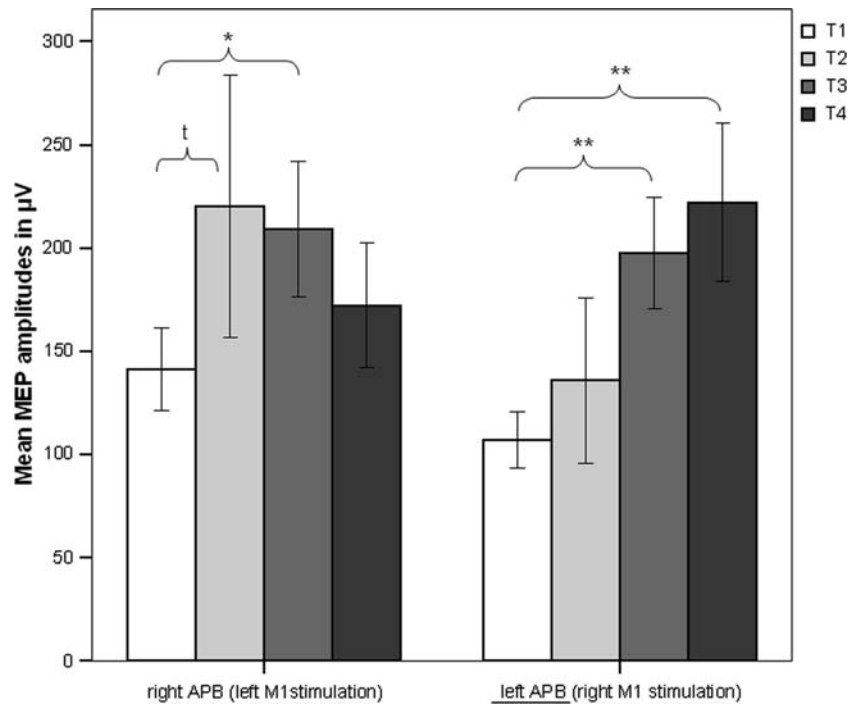
first five training sessions, the 'learning curve' did not reach a stable plateau before conclusion of the 2 weeks of training, suggesting at least a small potential for further gain. Interestingly, only training of the left thumb resulted in a decrease of ITI variability over time. The decrease of mean ITIs may therefore partly result from a smaller proportion of occasionally produced long ITIs which might have tampered the mean ITI before training. Our data are consistent with early behavioural studies proving hand asymmetry for mean ITIs and ITI variability (Annett et al. 1974; Hammond et al. 1988; Peters 1976). Moreover, Peters (1976) demonstrated a loss of asymmetry in tapping speed after prolonged practice of both hands. Generally, our behavioural data indicate the dominance of the right hand in all our subjects by revealing the greater effort required to gain speed in finger tapping when pretraining levels are already high. In contrast, more prominent changes can be induced at much shorter training intervals in the subdominant left hand because it is less proficient in fine-motor skills. The specific increase of regularity in tapping movements might be one factor which contributes to the larger training gains for the left thumb compared to the right.

Training-related increase of corticospinal excitability

To our knowledge, the current study is one of the first to investigate long-term training of an elementary finger movement using TMS. The majority of other pertinent studies to date have employed motor skill learning of more or less complex movements (e.g. finger movement sequences) over rather short training durations (Andres and Gerloff 1999; Classen et al. 1998; Cohen et al. 1998; Hazeltine et al. 1997; Karni et al. 1995; Nyberg et al.

2006; Pascual-Leone et al. 1994, 2005; Seidler et al. 2002; Shadmehr and Holcomb 1997).

Performance gains observed in the present study were accompanied by an increase of the mean amplitude of MEPs recorded from the trained muscle evoked by contralateral TMS. The amplitude of MEPs is an indicator of the level of excitability of the part of the corticospinal tract that controls the corresponding muscle and can therefore be used as a measure of motor training induced changes in corticospinal excitability. The increase in excitability is supposed to lead to a situation where the current spread from the stimulator gains access to more cortical units which contribute to increase the sum potential at the spinal neuron, thus resulting in a larger muscular response.

In interpreting the results, it is important to distinguish between synaptic changes within M1 (e.g. unmasking of previously silent synaptic connections; long-term potentiation or depression) and changes in the input to M1 from other structures—an aspect that is often neglected (Donoghue et al. 1990; Hallett 1995; Jacobs and Donoghue 1991; Ridding and Rothwell 1997). The current study design focused on changes within M1, making it impossible to determine whether alterations of synaptic functioning intrinsic to M1 or changes in the input to M1 increased the excitability of M1. We have however good reason to favour the former explanation. The tapping movement was performed at maximum speed with ITIs of ~200 ms. Toma et al. (2002) provide electrophysiological data suggesting that the rhythm of movements rather than each individual movement may be controlled at a movement rate of 3–4 Hz. This finding may support the idea of reduced involvement of motor regions typically associated with motor preparation and

makes an increase in tonic input from these regions rather implausible. Further support is provided by studies showing robust correlations between movement velocity and the intensity of the discharge pattern of M1 neurons (Ashe and Georgopoulos 1994; Humphrey 1972), indicating that the primary motor cortex is strongly involved in controlling the subjects' maximum tapping speed. Consistent with this is a recent study by Jäncke et al. (2004) demonstrating a decrease in maximum finger tapping speed following the disruption of M1 by low-frequency rTMS (Jäncke et al. 2004). In view of the preceding, we interpret our data as reflecting the increased involvement of M1 neurons in meeting the explicit requirement of gaining speed through tapping training. However, external influences from basal ganglia or cerebellum to M1 cannot be excluded and this needs to be addressed in further studies.

It is theoretically possible for the observed modulations of MEP amplitudes to result from excitability changes at the level of either the spinal cord or the peripheral nerve. By assessing CMAPs via supramaximal electrical stimulation of the median nerve (Rossini et al. 1994; Ziemann et al. 1998) we can rule out changes in peripheral nerve and muscle excitability. However, we cannot fully exclude changes at subcortical level, for example, brain stem or spinal cord. Nevertheless, we suggest the site where this form of plasticity takes place to be more likely of cortical than subcortical nature. Support for this hypothesis comes from a study by Muellbacher et al. (2001) showing that short-term practice of a repetitive ballistic pinch task led to a significant increase in MEP amplitude evoked by TMS, while MEP amplitudes evoked by direct stimulation of the corticospinal tract were not facilitated (Muellbacher et al. 2001). It is likely that these findings can be applied at least to the early MEP changes of the present study (Exp2-T2).

Although neural changes accompanying long-term training of elementary movements (e.g. finger tapping) have not been addressed so far, we try to place our results in the context of previous work examining training effects of complex motor skill learning. Given that conventional neuroimaging fMRI- and PET-based methods measure functional brain activation during the performance of movements and that TMS-based studies record amplitude of MEPs normally during complete muscular rest, a cross-method comparison of results is difficult. Neuroimaging studies on motor training will not therefore be considered here. To date there is one TMS study examining changes associated with longer motor training in healthy human subjects. In this study from Pascual-Leone et al. (1995), subjects practiced a finger movement sequence over the course of 5 days, this resulting in an enlargement of cortical motor areas that target those muscles involved in the practiced sequence. The motor training resulted also in a decreased activation threshold (Pascual-Leone et al. 1995). An increase in M1 excitability at posttraining measures has been shown also and consistently in TMS studies using much shorter training periods (one training session lasting several minutes up to 1 h) (Garry et al. 2004;

Hayashi et al. 2002; Muellbacher et al. 2001). Recent studies have been carried out to evaluate diverse motor trainings (mainly constraint-induced-therapy approaches) in stroke patients by means of TMS, and first results also suggest increased TMS motor map areas in the contralateral motor cortex following treatment, indicating increased excitability (Classen et al. 1998; Park et al. 2004). We assume that the increased corticospinal excitability which accompanied motor training in the present study is a necessary prerequisite for inducing plastic changes within the motor cortex—a condition that is present beyond the actual motor performance.

Ipsilateral M1 involvement during left-thumb training

Experiment 2 of the present study was designed to analyse motor cortex excitability in more detail across four time points. Special interest was placed on the involvement of the ipsilateral hemisphere. The existing literature emphasizes factors like *hand dominance* and *task complexity/difficulty* as playing a role in determining the involvement of the ipsilateral hemisphere during unimanual movements (Alkadhi et al. 2002; Baraldi et al. 1999; Caramia et al. 2000; Chen et al. 1997b; Cramer et al. 1999; Huang et al. 2004; Kawashima et al. 1998; Kim et al. 1993; Kobayashi et al. 2003; Sadato et al. 1996; Verstynen et al. 2005).

Our results show MEPs evoked from the left and right hemisphere M1 region to be differentially affected by the motor training throughout the course of 2 weeks. MEP amplitudes evoked from the contralateral right M1 were significantly enlarged at Exp2-T3 (*after 6 trainings*) and Exp2-T4 (*after 12 trainings*) but *not* directly after the first training session (Exp2-T2). Enhanced corticospinal excitability was also observed in case of left M1 stimulation; however, this effect was limited to the second and third time point of measurement (Exp2-T2, Exp2-T3). In line with previous studies (Beltramello et al. 1998; Kobayashi et al. 2003), our data thus suggest ipsilateral M1 activation during simple movements performed with the subdominant hand. We think that *effort*—as a consequence of task difficulty—may play a crucial role in our case. Subdominant thumb tapping in maximum speed is certainly associated with high processing demands on the motor areas since the left hand, and more so the left thumb, are much less skilled compared to the right hand in consistent right-handers. A very recent study by Lutz et al. (2005) reported cortical *rate effects* of similar magnitude for the subdominant and dominant hand, while at the same time showing lower tapping rates for the subdominant hand. This result led them to suggest that the subdominant motor cortex might operate at suboptimal control levels, although maximum neurophysiological activation has been reached during the maximum tapping task. Our data further suggest that the left motor cortex is particularly involved during the first training week. It is tempting to bring this finding, once again, in association with the left-hemisphere dominance in right-handers. It was shown that the subdominant hand produces a stronger rate effect in the contralateral

hemisphere than the dominant hand in paced finger tapping conditions (Jäncke et al. 1998). Thus, it was argued that the subdominant right motor cortex would have less processing capacities to control the subdominant hand during faster finger tapping rates (Jäncke et al. 1998, 1999). One could therefore speculate that the increase in excitability of the dominant left M1 reflects increased involvement at the beginning of training—at a time when the right-hemisphere motor system is not yet fully capable of controlling fast tapping movements. Based upon the results of their study, Agnew et al. (2004) hypothesize that 'the right hemisphere system is less skilled at controlling variable rate movements', and suggest further 'that the specialization of the left hemisphere corticostriatal system for dexterity is reflected in asymmetric mechanism for movement rate control'. We propose that the enhancement of MEPs after left M1 stimulation is triggered by the preceding exercise, and that this however represents a rather general increase of corticospinal excitation as a precondition for inducing more specific plastic changes at later stages of the parameter adaptation process.

We did not assess short-term changes of M1 excitability (e.g. after one training session) in the right-thumb training group. In order to provide an answer to the upcoming question whether the ipsilateral right M1 is involved in the beginning of right-thumb training, we refer to previous literature. It was repeatedly shown that the dominant M1 is involved in learning with the right and left hand while the subdominant motor cortex is exclusively active during learning with the subdominant hand, thus, providing evidence for an asymmetry of information transfer via the corpus callosum (Halsband 1992; Schulze et al. 2002). The TMS study by Pascual-Leone et al. (1995) investigating changes in M1 excitability following short-term motor training of the right hand also demonstrates a limitation of the facilitation effect to the left, trained M1 throughout the entire course of training (Pascual-Leone et al. 1995). Even though the involvement of the right M1 during right-thumb training seems implausible, particularly in the case of elementary tapping movements, this issue needs to be explored further.

Time course of neural excitability during motor learning

Current literature suggests that motor skill learning, and motor consolidation, is accomplished in at least two distinct stages—(1) a fast learning, initial, within-session improvement phase and (2) a slow learning phase, consisting of delayed, incremental gains in performance during continuing practice. While neurophysiological data has yet to provide a clear substrate for the first learning stage, slow learning has been consistently associated with marked increases in M1 activation (Ungerleider et al. 2002). After years of most intense motor skill training, musicians exhibit decreased activation when compared to unskilled subjects on comparable motor tasks, an effect that is commonly associated with diminished neural effort necessary to perform the movements. This is consistent with the idea that more neuronal involvement is needed at the beginning of training in order to build up a larger network or to implement task-specific routines. This increase in processing capacities is the basis for shaping more efficient networks at later training stages. The hypothesis seems plausible that the time course of neural excitability associated with motor training of simple repetitive tapping movements resembles that of more complex motor skill learning on a much shorter time scale. Based on our training protocol, we would predict an increase in M1 excitability during the first training days, followed by a decrease of excitability by the end of training as performance places less demand on cortical control. The design of experiment 2 with four measurement time points enables us to partly scrutinize the proposed hypothesis. However, data for the right hemisphere (contralateral to the trained hand) indicate continuously increasing MEP amplitudes. There is no decline in excitability after 2 weeks of training. This might indicate that the hypothesized process of expanding processing capacities is not completed in this case. Considering that tapping speed did not reach a stable plateau after 2 weeks of training, we argue that in our case incomplete training experience may explain the lack of a decline in motor cortex excitability at the end of training. We observed a pattern of changes in the left motor cortex (ipsilateral to the trained hand) which may fit the hypothesis of an increase of excitability in the first training week followed by a decrease after another training week. However, as already discussed, we suggest that the decline in left M1 excitation at the end of training is more likely an effect resulting from the slowly developing increase in processing capacities of the contralateral right motor cortex, which is predominantly associated with left hand movements.

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