Exp Brain Res (2003) 148:525–532
DOI 10.1007/s00221-002-1324-1

RESEARCH ARTICLE

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Pharmacological suppression of plastic changes in human primary somatosensory cortex after motor learning

Received: 22 May 2002 / Accepted: 25 October 2002 / Published online: 11 December 2002
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Abstract The strict division between motor and somatosensory systems might be less distinct than previously thought. Many brain mapping studies have described changes of somatosensory cortex (S-I) after the execution of a motor task, which supports the idea of a profound interconnectedness in the sensorimotor system. Here we report experiments in which we investigated by means of somatosensory evoked potentials (SSEPs) mapping the reorganizational capacities in primary somatosensory cortex before and after a Hebbian repetitive co-contraction task of the thumb and arm. We investigated the susceptibility of S-I plasticity to the pharmacological modulation of the GABA-neurotransmitter system by application of the $GABA_A$ agonist lorazepam. We found that repetitive training induced stable motor learning characterized by a significant improvement of performance. The time differences between the onset of contraction of the deltoid muscle and the abductor pollicis brevis were progressively shortened. The process of motor learning was accompanied by plastic changes in the primary somatosensory cortex as indicated by a significant increase in the dipole strength and a significant shift of the median nerve dipole on the hemisphere contralateral to the exercised side. Moreover, the individual shifts of median nerve dipole location were correlated with the individual improvement in motor performance. After administration of lorazepam, motor learning was significantly suppressed. The behavioural effect was accompanied by an abolition of the N20 dipole shift and an unchanged dipole strength. The results imply that motor learning leads to a profound reorganization in S-I which is subject to pharmacological suppression with the GABA agonist lorazepam.

Keywords SSEP mapping · Hebbian learning · Lorazepam · GABA agonist · Cortical plasticity

This research was supported by the Deutsche Forschungsgemeinschaft (Di 334/10–3 to H.D. and M.T.) and by a grant from the Heinrich-und-Alma-Vogelsang-Stiftung (to P.S.)

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Introduction

Based on the results of tests carried out on animals using a method involving fluorescent tracers, motor and somatosensory system seem to be connected by neuronal corticocortical projections (Porter 1992, 1997). A number of human brain mapping studies have recently described activation of somatosensory cortex after the execution of a motor task (Halsey et al. 1979; Kawashima et al. 1993; Kim et al. 1993; Rao et al. 1993; Mattay et al. 1998). Accordingly, the joint activation of both cortical regions supports the idea of a profound interconnectedness in the sensorimotor system. On the other hand, Rausch and coworkers suggested that the activation of human primary somatosensory cortex (S-I) might originate to a large extent from proprioception (Rausch et al. 1998).

Several studies have shown that training and learning can induce powerful changes in cortical organization which are highly task and modality specific (Pascual-Leone and Torres 1993; Elbert et al. 1995; Pantev et al. 1998; Sterr et al. 1998). There is agreement that the extent of cortical reorganization depends in part on the characteristics of the stimulus statistics (Fregnac et al. 1988; Wang et al. 1995; Cruikshank and Weinberger 1996; Godde et al. 1996). For example, repetitive training of hand muscles led to an enlargement (Cohen et al. 1995), while immobilization of leg muscles induced a decrease, in cortical representational areas (Liepert et al. 1995). Independent of the method of induction, there is also agreement that the degree of cortical reorganization

correlates with the parallel changes in behavioural performance. For the somatosensory system, Recanzone and co-workers found a direct relation between the degree of cortical plastic changes and the amount of improvement of psychophysically assessed discrimination performance (Recanzone et al. 1992). Similar results have been described for human somatosensory cortex (Pleger et al. 2001) and motor cortex (Nudo et al. 1992).

However, there is also evidence that specific forms of plastic cortical changes occur after less than 1 h of motor training (Cohen et al. 1995; Classen et al. 1998; Hallett et al. 1999; Tegenthoff et al. 1999; Bütefisch et al. 2000; Muellbacher et al. 2001). Accordingly, axonal sprouting is unlikely to explain this type of fast cortical reorganization. In contrast, functional mechanisms based on changes of synaptic efficacy have been advocated (Jacobs and Donoghue 1991; Pascual-Leone et al. 1995).

It has therefore been concluded that effects of training and learning should be subject to modulation by interfering pharmacologically with synaptic transmission. For example, glutamate, an excitatory neurotransmitter acting via *N*-methyl-D-aspartic acid (NMDA) receptors, should enhance cortical reorganization processes (Kano et al. 1991; Garraghty and Muja 1996; Tegenthoff et al. 1999).

As NMDA-receptor activation requires sufficient depolarization, the balance of excitation and inhibition is assumed to play a crucial role in synaptic plasticity. For example, the $GABA_A$-receptor system is directly involved in controlling and stabilizing long-term potentiation (Artola and Singer 1987; Luhmann and Prince 1990; Davies et al. 1991). Application of benzodiazepine has been shown to block LTP (del Cerro et al. 1992). In fact, interference with the $GABA_A$ system has been shown to successfully affect learning and training mediated plastic changes (Bütefisch et al. 2000).

In order to study the implications of Hebbian learning in the human motor system, so-called co-contraction tasks have been introduced (Cohen et al. 1995; Liepert et al. 1999; Tegenthoff et al. 1999; Schwenkreis et al. 2001b). In fact, since Hebb, and even since James, the aspect of simultaneity has become a metaphor in neural plasticity (James 1890; Hebb 1949). We used repetitive co-contraction of the thumb and arm involving the deltoid muscle and the abductor pollicis brevis (APB) to generate synchronous neural activity. Following this training, reproducible changes of the motor representation of the APB in human primary motor cortex (Cohen et al. 1995; Tegenthoff et al. 1999), and reorganization in primary somatosensory cortex (Schwenkreis et al. 2001b), have been demonstrated. Here we report experiments combining the co-contraction task with somatosensory evoked potential (SSEP) mapping to investigate how far the effects of motor learning and training-induced SI reorganization are susceptible to pharmacological interference with the GABAergic system by application of the GABA agonist lorazepam. We demonstrate that application of lorazepam blocks both training-induced behavioural improvement and parallel EEG changes in primary somatosensory cortex.

Materials and methods

Psychophysical tests

We tested 26 right-handed healthy subjects between 20 and 29 years of age (mean age = 24.7 years, ± 3.9 years). Twelve of them were first assigned to the lorazepam group, while the rest were treated using placebos. In addition, two subjects were investigated only under placebo condition.

The neurophysiological efficiency of lorazepam is based on an inhibition of corticocortical facilitation (Werhahn et al. 2002). This effect of lorazepam can be measured at 2 h and 5 h after intake, but no longer at 24 h (Ziemann et al. 1996). Therefore, lorazepam was administered in a single dose of 2.5 mg in rapid action form (FDDF) 2 h before starting the motor training in order to assure a sufficient neurophysiological effect. After an interval of 2 weeks, the drug and the placebo group were reversed and the procedure was repeated.

The aim was to learn a specific motor task consisting of a co-contraction of the deltoid and the APB muscle (Fig. 1). The subject was seated on a chair in a relaxed position with the monitor of the EMG equipment (Nihon Kohden Neuropack 8/Sensitivity 500 μV/Div) in front of the face to establish a visual feedback. The right upper arm was held in a relaxed position close to the right flank of the body, while the forearm and the hand were placed in front of the body in a right-angled position towards the upper arm (Fig. 1, left picture). The subject was instructed to act on demand ("on your marks", "get ready" and "go"). The aim was to perform an abduction of the thumb and an elevation of the upper arm as simultaneously as possible (Fig. 1, right picture). The subject had to perform three co-contractions per minute, resulting in a total of 180 movements in 60 min.

To judge the effects of the training, we measured the time differences between the onsets of the contractions of both muscles. EMGs were recorded non-continuously (Fig. 2). The subject was informed about the time difference after each movement in order to establish an auditory feedback

To evaluate the time course of learning, co-contractions (three repetitive movements per minute) had to be performed during six sessions over a period of 1 h (0–10 min, 10–20 min, 20–30 min, 30–40 min, 40–50 min, 50–60 min).

To investigate the influence of lorazepam on the subjects' attention we used a computer-based attention test (DAUF, Wiener-Testsystem, Version 3.00, Schuhfried, Mödling, Austria) (Schuhfried 1993). Rows of seven triangles are displayed on the screen in quick succession over 20 min. These triangles were pointed either upwards or downwards. Whenever three triangles were pointed downwards the subject had to press a reaction button. We evaluated the number of correct and incorrect answers as well as the reaction time. Subjects of both groups were tested after they had finished the 1 h of training.

SSEP measurement

We performed SSEP mapping in a subgroup of 12 subjects. Five subjects were first assigned to the drug group, and five to the placebo group. After 2 weeks, the groups were reversed. In addition, two subjects were investigated only under the placebo condition. Subjects were mapped before and immediately after termination of the motor task. To relate efferent output with afferent input we chose the median nerve for electrical stimulation, because of the close topographical relation to the APB muscle. We confined ourselves to median nerve mono-stimulation because of the difficulties in obtaining suitable axillary nerve SSEP responses as an afferent reference for deltoid muscle. A block electrode was placed on the median nerve at the wrist (Digitimer Stimulator DS9A, pulse duration: 0.1 ms; repetition rate: 3 Hz). Stimulation intensity was set to 2.5 times above the sensation threshold. Subjects had to report non-unpleasant prickling phenomenon in thumb, index and middle finger of the stimulated hand to verify correct positioning of stimulating

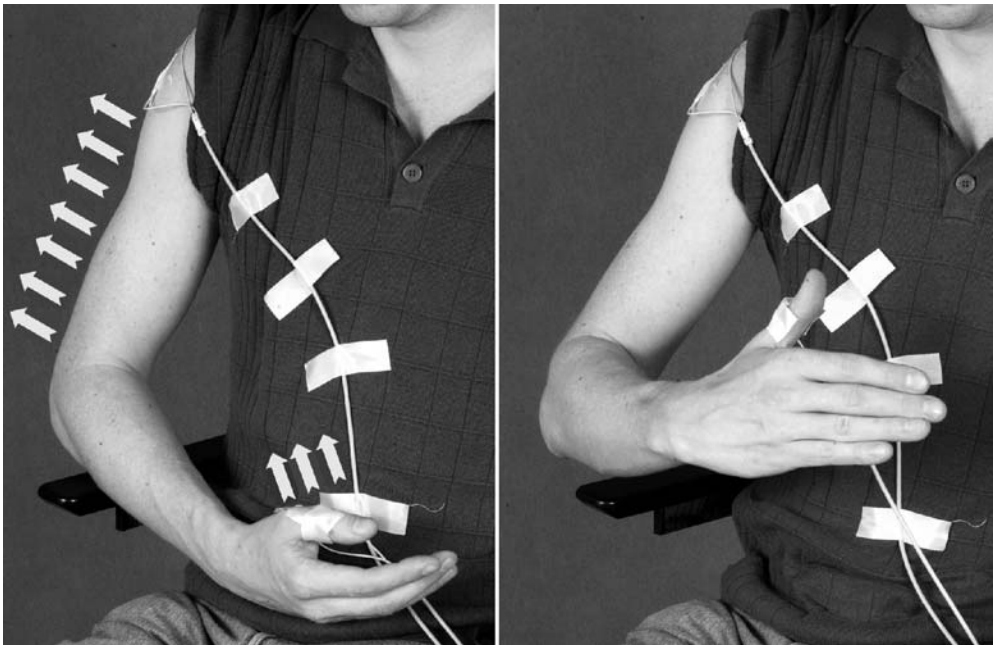

Fig. 1 Illustration of the motor task consisting of a co-contraction of the thumb and upper arm, left starting position, right end-position after co-contraction of the APB and deltoid muscles. *Arrows* indicate movement direction

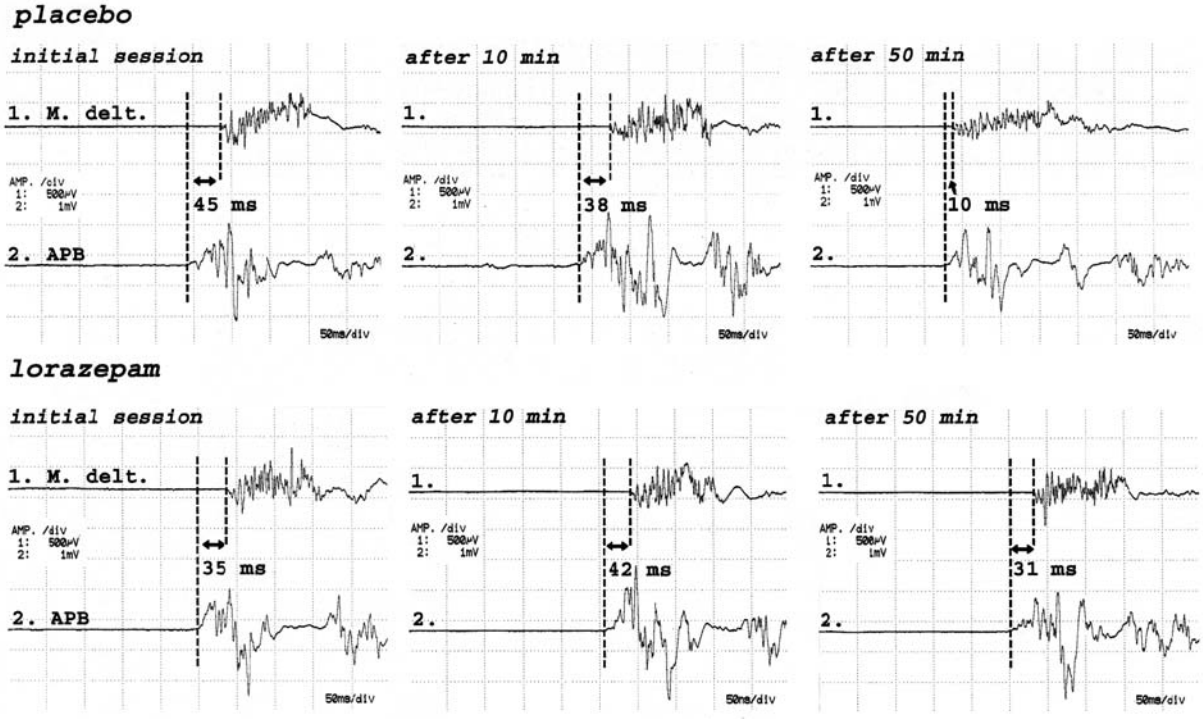

Fig. 2 Time differences between the onsets of contraction of the deltoid and APB muscles were determined using non-continuous EMG monitoring. The figure illustrates EMG data of one subject during motor learning in three different sessions (initial session, after 10 and after 50 min). *Vertical dashed lines* indicate onset of EMG, *numbers under each arrow* indicate time between the onsets of EMGs in milliseconds. *Top* Placebo condition showing a substantial shortening of the time difference between the onsets of EMGs of both muscles; *bottom* effect of lorazepam suppressing the shortening of the time differences observed under placebo conditions. Calibrations of EMG signals were 500 µV/div. for the deltoid and 1 mV/div. for the APB muscles

electrode. SSEP mapping was obtained from 32 scalp positions according to the 10–20 system (32-channel EEG system, Neuroscan, USA). Electrode positions were measured by means of a 3D digitizer (3D digitizer, Polhemus, Colchester, VT). In order to assure recording from identical locations before and after co-contraction, EEG electrodes were not removed between the pre- and postlearning sessions.

Electrical potentials (band-pass filtered between 1 and 1,000 Hz, sampling rate of 5,000 Hz) were recorded in epochs from 30 ms before to 100 ms after stimulus onset. A total of 1,600 stimulus-

related epochs were registered. SSEP processing was performed using the Neuroscan (Scan 4.1) and ASA software package (ANT software, The Netherlands). After registration, the epochs were digitally filtered using a band pass filter (20–500 Hz, 24 dB/Oct), referenced to a common average and averaged. For the source reconstruction we used a spherical three shell head model, which was fitted to the digitized electrode positions measured in each subject. Electric source reconstruction for the N20 component of the evoked potentials was performed by using a single rotating dipole model. Therefore, global field power (GFP) was calculated and the N20-SSEP component was fixed at the maximum of the first negative peak around 20 ms (mean 19.8 ms, ± 1.34 ms) using the ASA software package. In the rotating dipole model, the dipole coordinates are fixed in the time interval for which the fit is performed, while changes in the dipole orientation are allowed. The same procedure was used in our previous SSEP studies (Pleger et al. 2001; Schwenkreis et al. 2001a, 2001c).

The dipole's coordinates were projected onto an adjusted 3D-coordinate system (*y*-axis: joined acoustic meati of both ears; *x*-axis: joined centre point of *y*-axis and origin of nasion; *z*-axis: joined centre point and vertex). Changes in cortical representations were expressed by the difference of polar angle obtained pre- and postlearning (dipole position referred to the *z*-axis), and by the Euclidean distance between the dipole locations observed pre- and postmotor learning. Maximal dipole strength and goodness of fit (GOF) for the calculated N20 dipole were also compared pre/post. Data were statistically analyzed using ANOVA, Student's paired *t*-test and linear correlation analysis (Pearson's).

Results

Effects of motor learning

Subjects had to perform an abduction of the thumb and an elevation of the upper arm as simultaneously as possible (Fig. 1). To describe the differences in the motor performance between the placebo and the lorazepam groups we calculated the time differences between the contraction of the deltoid and the APB muscles for six successive training sessions over 1 h (Fig. 2). As shown in Figs. 2 and 3, the placebo group showed a significant improvement characterized by a reduction in time difference of –10.33 ms (SD: ±2.71 ms) during the first 10 min. This gain dropped to –3.41 ms (SD: ±0.95 ms) time difference in the next session, with a further reduction during the subsequent sessions (–3.1 ms, SD: ±0.92 ms; and –2.4 ms, SD: ±0.51 ms), reaching –2.06 ms (SD: ±0.59 ms) in the last session. In contrast during the first 10 min in the lorazepam group, there was an improvement of only –2.5 ms (SD: ±1.97 ms). During the successive sessions the reduction varied between –3.17 ms (SD: ±0.79 ms), –2.25 ms (SD: ±1.19 ms), –5.06 ms (SD: ±1.13 ms), and –2.72 ms (SD: ±0.90 ms).

An ANOVA for repeated movements was carried out and revealed that the time interval factor only had influence on the placebo group (placebo group: F=6.988, df=4, P<0.001; lorazepam group: F=0.731, df=4, P>0.05). In the placebo group, post hoc *t*-tests showed significant values for each time interval when compared with the first 10 min (P<0.05). In contrast, no significant values in the lorazepam sessions could be found (P>0.05).

In order to provide a subject-by-subject comparison, we recorded the results of ten subjects who participated in

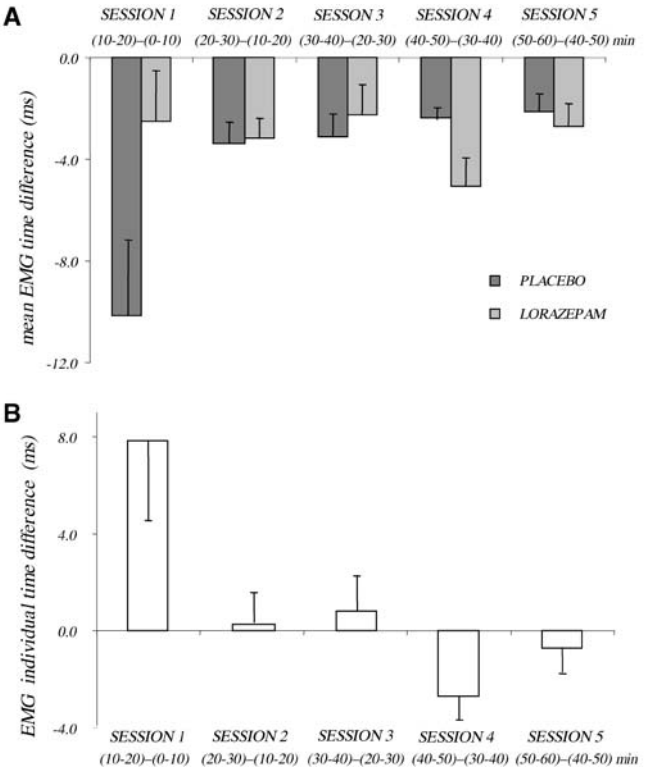

Fig. 3A, B Effects of the co-contraction task on the time differences between the onset of the contraction of deltoid and APB muscles measured at six successive sessions over 1 h (n=24). **A** Shown are the mean differences (±SEM) between successive sessions (10–20 to 0–10; 20–30 to 10–20; etc.) of the time differences between the EMG onset of both muscles for the placebo (*dark grey*) and the lorazepam (*light grey*) group (ANOVA for repeated measurements; placebo group: F=6.988, df=4, P<0.001; lorazepam group: F=0.731, df=4, P>0.05). **B** Mean subject-by-subject time differences (±SEM) expressed as the session-by-session difference

both test groups, i.e. the lorazepam group and the placebo group using a repeated-measures ANOVA with the within-subject factor session (0–10 min, 10–20 min, 20–30 min, 30–40 min, 40–50 min, 50–60 min) and drug (lorazepam and placebo) (ANOVA: F=4.167, df=4, P=0.004) (Fig. 3b). This analysis corroborated the findings described above: There was a large difference between the placebo and the lorazepam group only during the first 10 min of training (7.83 ms, SD: ±3.46 ms). Combined, only the placebo group showed a significant shortening of the time differences indicative for a training effect. Accordingly, lorazepam significantly eliminated the learning-induced improvement.

In the computer-based attention test we found no significant changes of pre- and postmotor learning with and without lorazepam application (mean average values of right answers: with lorazepam 119.4, SD: ±0.55, without lorazepam 119.6, SD: ±0.89, Student's paired *t*-test: P>0.05; false answers: with lorazepam 1.6, SD: ±1.3, without lorazepam 1.6, SD: ±1.6, Student's paired *t*-test: P>0.05; reaction time: with lorazepam 0.9 s, SD: ±0.14 s, without lorazepam 0.8 s, SD: ±0.07 s, Student's paired *t*-

test: $P>0.05$). Using the computer-based attention test we also investigated an age-matched control group comprising eight healthy subjects. We also found no significant changes in error statistics and reaction time 2 h after the administration of 2.5 mg lorazepam (FDDF) (mean average values of right answers: with lorazepam 117.6, SD: ±2.13; without lorazepam 118.3, SD: ±2.12, Student's paired *t*-test: $P>0.05$; false answers: with lorazepam 2, SD: ±1.69, without lorazepam 1.6, SD: ±0.92, Student's paired *t*-test: $P>0.05$; reaction time: with lorazepam 0.74 s, SD: ±0.18 s; without lorazepam 0.75 s, SD: ±0.15 s, Student's paired *t*-test: $P>0.05$).

SSEP mapping

The effects of motor learning in the 12 subjects mapped neurophysiologically were in the same range as those described above for the total of 26 subjects. In order to study changes in the median nerve representation of the primary somatosensory cortex, we calculated the N20 dipole locations before and after motor learning obtained from SSEP mapping following electrical stimulation of the median nerve of both sides. For the placebo group, we found a significant shift of the dipole location after repetitive co-contraction on the left hemisphere which underwent motor learning. The Euclidean distance between the dipole for the median nerve of the right side pre- to postmotor learning was significantly larger (mean 7.66 mm, SD: ±3.3 mm) than the pre-post distance on the right hemisphere (mean 3.13 mm, SD ±1.5 mm; ANOVA: $F=36.249$, $P>0.001$; Table 1). In addition, in the left hemisphere the polar angle of the N20-dipole locations decreased after motor learning (29.2°, SD: ±4.5° pre vs. 27°, SD: ±3.9° post; ANOVA: $F=12.679$, $P=0.004$). By contrast, in the right control hemisphere after motor learning no changes of the polar angle of the N20-dipole locations were found (27.1°, SD: ±4.5° pre vs. 26.9°, SD: ±4.7° post; ANOVA: $F=0.568$, $P=0.467$; Table 1). These results indicate a medial and superior shift on the postcentral gyrus of the left hemisphere representing the median nerve of the exercised side, but no changes on the contralateral hemisphere. Additionally, we found a significant increase in dipole strength after motor learning on the hemisphere contralateral to the exercised side (ANOVA: $F=5.039$, $P=0.046$; control side: $F=0.201$, $P=0.663$), while the GOF pre- and postmotor learning showed no changes (ANOVA: $F=0.799$, $P=0.391$; control side: $F=0.144$, $P=0.712$).

After the administration of lorazepam, the Euclidean distance on the left hemisphere between the N20 dipole pre- and postmotor learning was not significantly altered (mean 3.4 mm, SD: ±1.9 mm) compared to the pre-post distance on the right hemisphere (mean 4.4 mm, SD: ±3.6 mm; ANOVA: $F=1.034$, $P=0.336$; Table 1). In addition, we found no significant changes in the polar angles on both hemispheres after motor learning (exercised side: 25.4°, SD: ±3.7° pre vs. 25.8°, SD: ±3.6° post; ANOVA: $F=1.78$, $P=0.215$; control side: 24.7°, SD: ±3.3°

Table 1 SSEP mapping data of the trained (T) and control (C) hemisphere pre- and postmotor learning, for the placebo and lorazepam groups ($n=10$)

		Polar angle pre-post shift (°)		Euclidean distance pre-post (mm)		Dipole strength (nAm) pre		Dipole strength (nAm) post		N20 (ms) pre		N20 (ms) post		GOF (goodness of fit) (%) pre		GOF (goodness of fit) (%) post	
		T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Placebo	Mean	2.25	0.21	7.66	3.13	6.94	9.68	11.1	9.29	19.8	19.2	20.3	19.4	96.5	97.2	96.8	97.5
	SD	2.19	1.00	3.31	1.57	4.81	4.42	5.35	3.63	1.52	1.41	0.98	1.47	1.42	1.45	2.40	1.46
Lorazepam	Mean	0.36	0.42	3.42	4.40	6.94	6.84	6.18	7.15	19.9	19.6	19.8	20.0	97.0	95.9	96.4	96.5
	SD	0.86	1.67	1.87	3.60	1.89	4.06	2.24	1.96	1.13	1.24	1.09	1.83	1.21	2.36	2.26	1.70

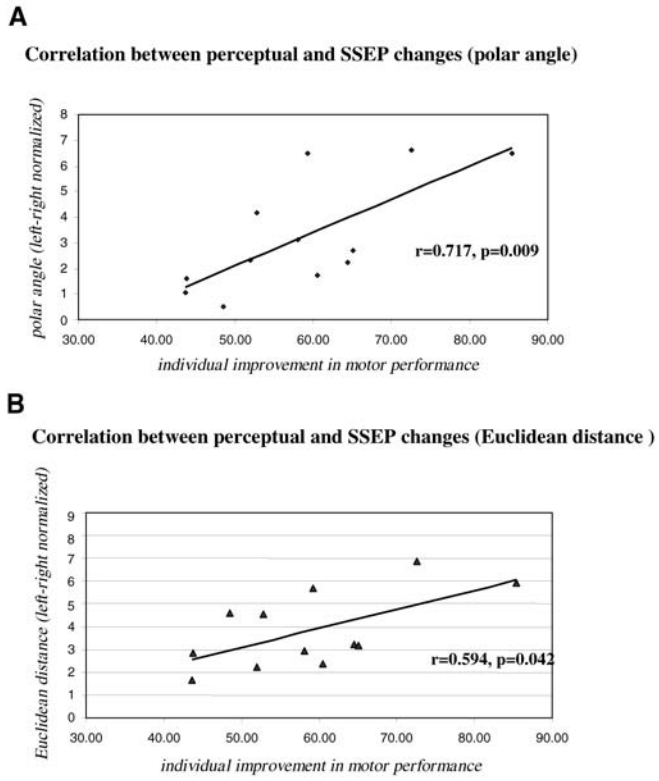

Fig. 4A, B The figures show the scatter plots of correlation analyses between the perceptual and SSEP changes. **A** Linear correlation analysis (Pearson's) revealed a significant positive correlation between the shift of the dipole as expressed by the polar angles (left-right normalized, right shift was subtracted from left shift) and the individual improvement in motor performance (expressed as total reduction in time difference between the onset of EMG responses normalized to the time difference observed during the initial session [(0–10 min)–(50–60 min)/(0–10 min)] under placebo conditions (r=0.717, P=0.009, n=12). **B** We also found a significant positive correlation between motor learning and enlarged Euclidean distances (r=0.594, P=0.042, n=12)

pre vs. 25.1°, SD: ±3.2° post; ANOVA: F=0.635, P=0.446; Table 1). The dipole strength and the GOF pre- and postmotor learning were not affected either (dipole strength: exercised side: ANOVA: F=3.323, P=0.102; control side: ANOVA: F=0.147, P=0.711; GOF: exercised side: ANOVA: F=1.531, P=0.247; control side: ANOVA: F=1.022, P=0.338).

Correlation between perceptual and SSEP changes

The amount of behavioural improvement was variable throughout the individuals (cf. the substantial variability present in Fig. 3a, b). Under the assumption that SSEP changes might be related to changes in motor learning, we hypothesized that the observed shifts in dipole localization should correlate with the changes in individual motor performance. Linear correlation analysis (Pearson's) revealed a significant positive correlation between shifts in dipole position (left-right normalized; shift on the right subtracted from shift on the left hemisphere) and the individual improvement in motor performance (expressed as total reduction in time difference between the onset of EMG responses normalized to the time difference observed during the initial session [(0–10 min)–(50–60 min)/(0–10 min)] under placebo conditions (r=0.717, P=0.009, n=12; Fig. 4a). This relationship was corroborated by a significant positive correlation (r=0.594, P=0.042, n=12; Fig. 4b) between motor improvement and the enlarged Euclidean distances (left-right normalized as mentioned above). In contrast, under lorazepam, no correlation between behavioural performance and dipole shifts could be found (Euclidean distance: r=–0.43, P=0.453; polar angle: r=0.106, P=0.386, n=10). Accordingly, a slight gain in motor performance was associated with small changes of the N20-dipole locations in primary somatosensory cortex. On the other hand, those subjects who showed a large cortical reorganization also showed a large effect of motor learning. This correlation implies that the presence of a substantial behavioural variability is well reflected in a corresponding variability of cortical organization.

Discussion

We found that repetitive motor training consisting of an abduction of the thumb and an elevation of the upper arm as simultaneously as possible induced stable motor learning. The improvement of the motor performance over a time period of 1 h was quantified by measuring the time differences between the onset of the contraction of the deltoid muscle and the abductor pollicis brevis, which showed a progressive shortening. As shown by SSEP mapping, the process of motor learning was accompanied by plastic changes in the primary somatosensory cortex as indicated by a significant shift in the median nerve dipole and a significant increase in the dipole strength on the hemisphere contralateral to the exercised side. These findings confirm the results described in a previous study (Schwenkreis et al. 2001a). Here we demonstrate a significant suppression of this motor learning after the administration of lorazepam, a $GABA_A$-receptor agonist (Ziemann et al. 1996). Most interestingly, the suppression of the behavioural effect was accompanied by a complete abolition of the N20-dipole shift after median nerve stimulation as typically observed in the placebo group, and by a lack of change in dipole strength. Further the significant positive correlation between the shift of the dipole as expressed by the polar angles (Fig. 4a) and the Euclidean distances (Fig. 4b) and the parallel relative improvement in motor performance found under placebo conditions was lost under lorazepam.

Fast occurring cortical plasticity is thought to be based on changes in synaptic efficacy arising from decreasing afferent-driven inhibition and the establishment of latent pre-existing synaptic connections (Alloway et al. 1989; Jacobs and Donoghue 1991). NMDA-receptor activation requires sufficient depolarization; therefore, the balance

of excitation and inhibition is assumed to play a crucial role in synaptic plasticity (Artola and Singer 1987; Luhmann and Prince 1990; Davies et al. 1991). On the other hand, fast occurring cortical reorganization after learning a motor task has been thought to be related to excitability changes of GABA-mediated lateral interneurons (DeFelipe et al. 1986; Garraghty and Muja 1996; Ziemann et al. 1996; Rijntjes et al. 1997).

In a recent study on sensory coactivation we have shown that pharmacological treatment of human subjects with lorazepam completely wiped out the coactivation-induced reorganization as well as the parallel changes in perceptual thresholds (Dinse et al. 2001). In fact, the application of benzodiazepines has been shown to block LTP in brain slices of hippocampus and piriform cortex (del Cerro et al. 1992). We suggest that the blocking observed in this study and in the experiments described here is due to a hyperpolarizing effect of lorazepam, making it more difficult to reach threshold for inducing plastic processes.

Comparable considerations have been formulated for human motor cortex. Cohen and co-workers reported reproducible changes of the motor representation of the APB in human motor cortex after synchronous movements of hand and shoulder (Cohen et al. 1995, 1996). Using a similar motor task, Tegenthoff and co-workers described a suppression of training-induced plastic changes in human motor cortex after the administration of lorazepam (Tegenthoff et al. 1999).

Substances such as lorazepam used in this study might evoke severe side effects. We therefore used a conventional attention test (Schuhfried 1993) to investigate whether lorazepam treatment affected attention. According to this analysis, no differences were observed for the control and lorazepam group, indicating that the drug did not evoke any unspecific side effects.

Our results showed representational changes of the primary somatosensory cortex consisting of a significant shift in the median nerve dipole and a significant increase in dipole strength during a motor learning co-contraction task, a training-induced reorganization that could be suppressed by lorazepam. We suggest that the reorganization of the primary somatosensory cortex in our study, which is controlled by the GABAergic system, is due to changes in the proprioceptive inputs induced by the repetitions of the co-contraction of the deltoid and the APB muscles. This view is consistent with the data of Rausch et al., who concluded that activation of somatosensory cortex during the active movement and the passive stimulation of fingertips is likely to originate to a large extent from proprioception (Rausch et al. 1998).

When comparing these results to recent coactivation experiments performed in the sensory system (Pleger et al. 2001), one has to consider that in the tactile coactivation experiment, tactile stimuli used for coactivation were applied completely passively. In contrast, in the present co-contraction experiments subjects intentionally initiated movements. Accordingly, there is a cognitive aspect related to intention and motor planning that is missing in the tactile coactivation experiments. Further experiments employing a similar passive method of movements might reveal further insights into these types of plastic changes and its mechanisms. Also, the perceptual consequences of motor training-induced changes in S-I have to be elucidated.

Combined, our results show that the application of lorazepam suppresses the co-contraction-induced improvement in motor performance as indicated by a reduction in time differences between coactivated muscles and the median dipole shift in primary somatosensory cortex with no changes in dipole strength. These findings suggest that a pharmacologically induced enhancement of the $GABA_A$-mediated inhibition has severe effects on plastic changes in the motor system that secondarily influences primary somatosensory cortex by reducing proprioceptive input.

We found motor-learning-induced plastic changes of the primary somatosensory cortex described by a significant shift in the median nerve dipole and a significant increase in dipole strength on the hemisphere contralateral to the exercised side only. These findings provide further evidence that the motor and somatosensory cortex act in concert as one functional network. Lorazepam as a $GABA_A$-receptor agonist is able to block these plastic changes both behaviourally and neurophysiologically by interfering with synaptic functions.

Acknowledgements We thank Mrs. R. Essoh for skilful editing of the manuscript.

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