Exp Brain Res (2000) 130:48–59

RESEARCH ARTICLE

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Cutaneomotor integration in humans is somatotopically organized at various levels of the nervous system and is task dependent

Received: 25 August 1998 / Accepted: 11 June 1999

Abstract Integration of tactile afferent signals with motor commands is crucial for the performance of purposeful movements such as during manipulation of an object in the hand. To study the somatotopic organization of sensorimotor integration we applied electrical peripheral conditioning stimuli to a digit located near (homotopic stimulation) or distant from (heterotopic stimulation) relaxed or isometrically contracted intrinsic hand muscles at variable time intervals prior to transcranial magnetic stimulation (TMS). Cutaneous stimulation has previously been shown to modulate the amplitude of the motor evoked potential (MEP) and to shorten the duration of the silent period (SP) evoked by TMS. In relaxed target muscles the time-dependent modulation of TMS-evoked motor responses by homotopic conditioning stimulation differed from modulation by heterotopic stimulation. Similar differences in the modulation pattern evoked by homotopic and heterotopic conditioning stimulation were observed for two distinct target muscles of the hand (abductor digiti minimi, abductor pollicis brevis muscle). Differences in modulation were maximal when the conditioning stimulation was applied 25–30 ms and 150–200 ms prior to TMS. Comparison of the modulation of the amplitudes of MEPs evoked by transcranial electrical stimulation (TES) and the modulation of those evoked by TMS suggests that differences between homotopic and heterotopic stimulation originate subcortically at 25- to 30-ms and, at least partially, cortically at 150- to 200-ms interstimulus intervals. In isometrically contracted intrinsic hand muscles the degree to which the SP was shortened reflected the location and the timing of the conditioning stimulus. Shortening was maximal when the conditioning stimulus was applied nearest to the contracted target muscle and 20 ms prior to the test stimulus. In contrast to the SP duration, the MEP size in voluntarily contracted target muscles was unaffected by the location of the conditioning stimulus. The somatotopic gradient of SP shortening was abolished when the two target muscles were simultaneously activated isometrically. Together, our findings suggest that somatotopy of input-output relationships is implemented at both a spinal and a cortical level in the human central nervous system and may also depend on the motor task involved.

Key words Somatotopy · Input-Output · Inhibition · Excitation · Transcranial magnetic stimulation

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Introduction

Manipulative actions such as tactile exploration require the integration of cutaneous afferent information with efferent motor commands. It has long been known that information from cutaneous receptors can modulate motoneuronal activity (Asanuma et al. 1968; Lemon 1981; Wiesendanger 1973). In humans a concept of multilevel cutaneomotor integration has emerged from neurophysiological studies employing cutaneomuscular reflexes or peripherally conditioned transcranial magnetic stimulation (TMS). Cutaneomuscular reflexes (Caccia et al. 1973; Chen and Ashby 1993; Jenner and Stephens 1982) refer to the complex sequence of excitatory and inhibitory phases in the electromyography (EMG) of voluntarily contracted distal upper limb muscles that is induced by cutaneous stimulation of the digits. Lesion studies have suggested that early excitatory and inhibitory components, termed E1 and I1, are generated at a spinal level,

and a later excitatory component, E2, at a supraspinal and possibly a cortical level (Chen and Ashby 1993; Jenner and Stephens 1982), although the latter conclusion has been questioned by others (Palmer and Ashby 1992). Experiments employing transcranial stimulation methods (Clouston et al. 1995; Maertens de Noordhout et al. 1992; Ohki et al. 1994) have generally confirmed multiple levels of cutaneomotor integration, but some of these studies, including those utilizing natural stimuli, have cast some doubt on previous conclusions about the level at which specific components of cutaneomuscular reflexes are generated (Macefield et al. 1996; Maertens de Noordhout et al. 1992).

Whereas the above studies have focused on the direction and amplitude of cutaneous modulation in active or contracted muscle, its somatotopic organization, another important aspect of cutaneomotor integration, has received much less attention (Caccia et al. 1973; Chen and Ashby 1993; Deuschl et al. 1995; Terao et al. 1995). This is surprising because in natural movements, such as those intended to collect sensory information in tactile exploratory behavior, a cutaneous stimulus may facilitate one muscle while inhibiting the other, and therefore the behavioral effect of such a stimulus cannot be completely deduced from the net excitation or inhibition of a single muscle. Similarly, the spatial gradient at which neuronal elements controlling synergistic muscles are subject to modulation by afferent stimulation may depend on the motor task that they are involved in. To address these issues the somatotopic organization of cutaneomotor integration was systematically explored in the resting and active human hand in a conditioned TMS paradigm.

Preliminary accounts of the results have been published in abstract form (Classen et al. 1996; Steinfelder et al. 1998).

Methods

Experiments were performed on 36 subjects (21 men, 15 women; age 32±11 years). All subjects were right-handed except three who were left-handed, according to the Oldfield handedness inventory (Oldfield 1971), and all had normal results on physical and neurological examinations, and gave their written informed consent. The protocol was approved by the NINDS Institutional Review Board and the Ethics Committee of the University of Rostock.

Recording

Surface EMG activity was recorded from the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles of the dominant hand. EMG signals were amplified using a Dantec Counterpoint electromyograph (Dantec, Medical A/S, Skovlunde, Denmark), or a Toennies Myograph IIR (Toennies, Freiburg, Germany) and bandpass filtered between 20 and 1000–3000 Hz. EMG signals were digitized at a frequency of 3 or 5 kHz using an A/D converter and stored on a personal computer for later off-line analysis.

For somatosensory evoked potentials electroencephalographic signals were recorded from C3' using a reference at Fz (silver/silver chloride – electrodes placed according to the international 10/20 system; bandpass filtered between 1 s and 2 kHz; sampling rate 4 kHz).

Stimulation

TMS was performed with a custom-built Cadwell magnetoelectric stimulator (Cadwell Laboratories, Kennewick, Wash., USA) or a Magstim 200 (Magstim, UK). An eight-shaped magnetic coil (diameter of each wing: Cadwell 4.5 cm; Magstim 7.0 cm) was used with the handle pointing backwards and laterally at an angle of 45° to the sagittal plane. The optimal scalp position for activation of APB was determined and marked directly on the scalp with a soft-tip pen. Briefly, the magnetic coil was moved about with its center at around 5 cm lateral and 1 cm anterior to Cz using stimulus intensities of approximately 60% of maximal stimulator output MSO, which evoked a clearly discernible response amplitude in the resting APB. At the site yielding the maximum amplitude for APB the threshold was determined as the minimal stimulator intensity producing a response amplitude of at least 50 µV amplitude in at least five of ten trials.

Electrical brain stimulation (TES) was performed using a Digitimer D180 (maximum stimulator output 750 V, 1 A; Digitimer, Welwyn Garden City, UK). The anode was placed 6 cm lateral to the cathode, which was placed on the vertex.

In experiments on resting target muscles (experiment 1, see below), peripheral cutaneous electrical stimulation was performed using a standard commercial stimulation block (Ag/AgCl; distance between anode and cathode 2.5 cm) connected to a Dantec Counterpoint or Cantata (Dantec). Single conditioning electrical stimuli (width 200 µs) were applied at 200% perceptual threshold to the radial side of dig. I or the ulnar side of dig. V. A stimulation was termed homotopic, if the conditioning stimulus (CS) was applied to a region near the target muscle, and heterotopic, if the stimulus was delivered to a site distant from the target muscle. For example, conditioning stimulation of dig. V was homotopic for ADM and heterotopic for APB. Subjects were instructed to keep the target muscles at complete rest during the experiment. Relaxation was monitored by visual and auditory feedback.

In experiments on tonically activated target muscles (experiment 2, see below), cutaneous stimulation was performed using ring electrodes around the proximal phalanges of dig. I to dig. V at 300% of the perceptual threshold.

For somatosensory evoked potentials (SSEPs) ring electrodes around the proximal phalanx of dig. I were used at 300% of the perceptual threshold and at a stimulation frequency of 3.0 Hz. Three averages of 200 trials each were collected.

Experimental design

Relaxed target muscles (experiment 1)

Starting from the optimal point of stimulating the APB muscle, the intensity of the magnetic stimulator was adjusted, and the position of the coil was moved slightly so as to produce an unconditioned response amplitude in the APB or ADM of 0.5–1.5 mV. This stimulus intensity was 121±8% of RMT of the APB. Experiments were performed in blocks of 40 trials. In 10 of the 40 trials test stimuli were given alone (control). In the remaining 30 trials conditioning stimuli were applied at one of three different interstimulus intervals (ISIs). All four conditions (control and 3 ISIs) were pseudorandomly intermixed. To keep the subject awake and to ensure attention to the experiment, subjects were asked to indicate verbally after the magnetic pulse whether they had felt a conditioning electrical stimulus. Intertrial intervals were at least 5 s.

The experiment was conducted on 14 subjects and compared the effects of cutaneous afferent stimulation of dig. I and dig. V on modulation of the MEP amplitudes of APB and ADM at various intervals between conditioning and test stimuli. ISIs of 16, 18, 20, 21, 22, 25, 30, 40, 50, 60, 75, 100, 125, 150, 175, 200, 225, 250, 300, 400, and 500 ms were tested. Experiments were conducted in a single session on nine subjects and in two or three sessions on the remaining subjects.

The effects of peripherally conditioned TES and TMS were compared in heterotopically and homotopically conditioned APB

and ADM in seven subjects. Stimulus intensities averaged 75.1±10.7% of maximal electrical stimulator output using a stimulus width of 100 µs. The intensity of the electric stimulator was set to produce an MEP amplitude of between 0.5 and 2 mV in APB and ADM. Four blocks, consisting of 40 trials each, were performed. In each block 20 unconditioned test stimuli (10 TES and 10 TMS) were randomly intermixed with 20 conditioned stimuli (10 TES and 10 TMS) in which the test stimulus followed the CS at 25, 30, 150, or 200 ms.

Contracted target muscles (experiment 2)

Subjects were asked to contract the target muscle(s) at about 15% of maximal isometric voluntary force by abducting dig. I, or dig. V against a force transducer (range 0–100 N, nonlinearity less than 1%, contact surface area 0.7×1.8 cm) wired for feedback into an oscilloscope. The intensity of the magnetic stimulator was adjusted to produce a silent period in the contracted target muscle (APB or ADM) which ended at about 170 ms following the magnetic stimulation.

In the first series the effects of a homotopically (dig. I) or heterotopically (dig. V) applied CS on the MEP size and SP duration evoked in the APB was investigated as a function of the interstimulus interval in ten subjects. Interstimulus intervals of –50 ms (CS following test stimulus) and 10, 17, 20, 22, 25, 30, 50, 100, and 175 ms (CS preceding test stimulus) were tested. For each interval ten control trials (no conditioning stimulation) were followed by two sets of ten conditioned trials each. The order of the two sets of conditioned trials (homotopical or heterotopical conditioning stimulation first) varied randomly between subjects. The order in which the various ISIs were tested also differed randomly between subjects.

The somatotopic gradient of modulating the SP by peripheral conditioning stimulation was investigated in detail in 11 subjects by applying conditioning stimuli to the proximal phalanx of dig. I, II, III, IV, or V. Ten control trials (no conditioning stimulation) were performed prior to five sets of ten conditioned trials, in which the CS to a digit was delivered 20 ms prior to the test stimulus. The order of the sets, i.e., the order of the digits to which the conditioning stimuli were applied, was counterbalanced between the subjects. First, a full sequence was completed using the APB as the target muscle. In a second session the ADM was the target muscle.

The effect of a simultaneous contraction of two target muscles (APB and ADM) on the somototopical gradient of SP shortening was examined in eight individuals. The subjects were asked to push a bar isometrically against a force transducer by simultaneous abduction of APB and ADM such that the combined action produced 15% of the combined maximal force. Conditioning stimuli were applied at either dig. I or dig. V. The effects of conditioning stimuli applied homotopically were compared with those applied heterotopically. Ten control trials (no conditioning stimulation) were followed by four sets of ten conditioned trials each. In five sessions the sequence of the four sets began with conditioning stimulation at dig. I, followed by sets conditioned at dig. V, dig. V, and dig. I; in the other four sessions, conditioned stimulation began at dig. V followed by sets conditioned at dig. I, dig. I, and dig. V.

To enable comparison between the timing of somatotopic gradients with the time of arrival at the somatosensory cortex as judged by the N22 component of the SSEPs following digit stimulation, we performed SSEP measurements in the same subjects. In each subject the latency of the N22 was determined as the mean of the N22 of the three SSEPs collected. The N22 averaged to 22.3±0.8 ms.

Statistical analyses

In all analyses the level of significance was set to $P<0.05$.

Experiment 1

MEP amplitudes were measured peak-to-peak. For each block, mean MEP amplitudes were calculated for each of the four conditions (control and three ISIs). Mean conditioned MEP amplitudes are expressed at each ISI as a percentage of the mean control amplitude of the corresponding block. The null hypothesis of a normal distribution of the individual means of all subjects could not be rejected by statistical testing at any of the individual ISIs (Kolmogorov-Smirnov; $P>0.05$), thus supporting the assumption of a normal distribution of the data.

Heterotopic and homotopic cutaneous conditioning stimulation were compared pairwise for two target muscles and for the corresponding sites of cutaneous stimulation using a repeated measures analysis of variance (rmANOVA; site × muscle × ISI; 2×2×21) with site (homotopic, heterotopic) as the site of peripheral cutaneous stimulation, muscle (APB, ADM) as the target muscles, and ISI (16, 18, 20,... 500) as the interstimulus interval between cutaneous afferent stimulation and TMS.

To compare the modulation of TES- and TMS-evoked MEPs the mean size of homotopically or heterotopically conditioned MEPs is expressed as a percentage of the mean of unconditioned MEPs. Results from homotopic or heterotopic stimulation are combined for 25 and 30 ms (short ISIs), and 150 and 200 ms (long ISIs) for each individual subject tested. A repeated measures ANOVA (type × latency × site, 2×2×2) was performed with type (TES, TMS) as the stimulation technique, latency (short, long) as the timing of the conditioning peripheral stimulus in relation to the transcranial stimulation, and site (homotopic, heterotopic) as the location of the conditioning stimulus. To test specific hypotheses (see "Results") paired *t* tests were additionally employed.

Experiment 2

MEP size was measured peak-to-peak. The duration of the SP was defined as the time between the reappearance of EMG activity following TMS and the MEP onset in control trials. Typically, in control trials, the MEP began at about 20 ms, and the SP ended at about 170 ms following the magnetic stimulation yielding a SP duration of 150 ms. For each subject SP durations were averaged for each set.

In the first series data were analyzed using a two-way rmANOVA (ISI (-50, 10... 175), site (homotopic, heterotopic)). In the second series a correlation analysis was performed between the order of the digit stimulated and the grand averages of SP durations of APB or ADM. In the third series a two-way rmANOVA [muscle (APB, ADM), site (homotopic, heterotopic)] was performed. Separate analyses were carried out in all series for MEP size and SP duration, respectively.

Results

Observations in relaxed target muscles (experiment 1)

In accordance with results obtained by other investigators (Clouston et al. 1995; Maertens de Noordhout et al. 1992) we found that MEP size can be facilitated or attenuated by afferent cutaneous stimulation. With both homotopic and heterotopic stimulation the direction of the modulation (i.e., facilitation or attenuation) depended on the exact timing of the conditioning peripheral stimulus in relation to the timing of the cortical magnetic pulse. With homotopic stimulation of APB the excitatory and inhibitory phases of modulation alternated, and a general pattern emerged consisting of a brief early (ISI ca. 16–22 ms) excitatory phase, brief early (ca. 25–50 ms) in-

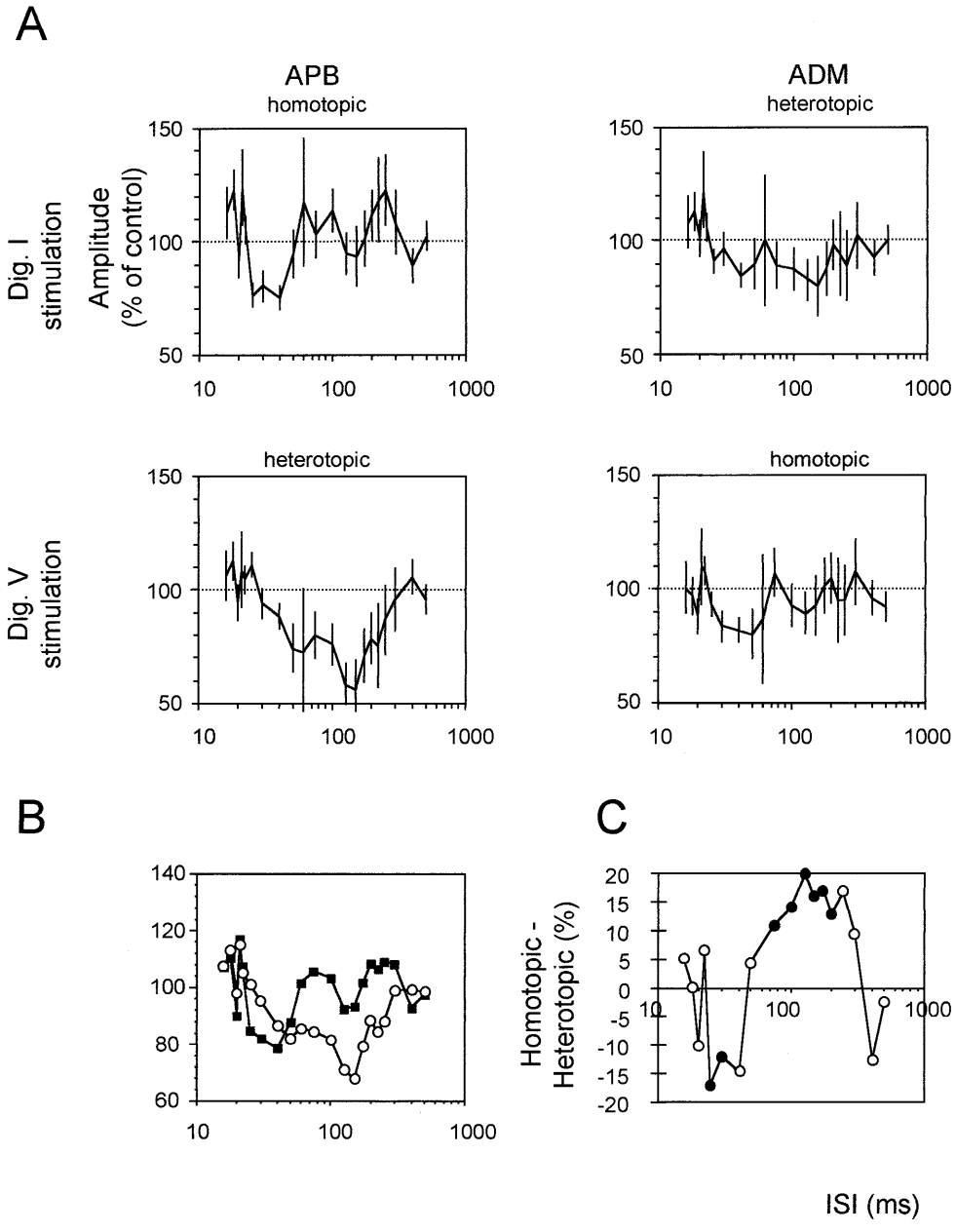


Fig. 1 **A** Time course of modulation of normalized MEP amplitude of APB and ADM by homotopic and heterotopic conditioning cutaneous stimulation. Results from 14 subjects. Data indicate mean±SEM. **B** Pooled results of modulation of MEP size of APB and ADM by homotopic (*open symbols*) or heterotopic (*filled symbols*) conditioning cutaneous stimulation at the radial side of dig. I or ulnar side of dig. V. **C** Difference of normalized MEP amplitudes (heterotopic minus homotopic stimulation). *Filled circles* significant differences between homotopic and heterotopic stimulation at 25 and 30 ms and 75–200 ms ($P<0.05$)

hibitory phase, brief intermediate (ca. 75–125 ms) excitatory phase, and a late (ca. 250–300 ms) excitatory phase (Fig. 1A). Occasionally the intermediate brief excitatory phase was missing, and this resulted in a longer inhibitory phase. This pattern was similar in ADM (Fig. 1A). Heterotopic stimulation modulated MEP amplitudes differently than homotopical stimulation but was similar in APB and ADM. Typically the inhibition seen in the homotopically stimulated muscle at short ISIs was less pronounced or replaced by a facilitation in the heterotopically stimulated muscle. At longer ISIs the heterotopically stimulated muscle was more inhibited than the homotopically stimulated muscle, which was either facilitated or mildly inhibited. An example of homotopic and heterotopic conditioning stimulation on MEPs in APB is shown in Fig. 2. Statistically significant effects were found in all of the subjects for individual ISIs. However, the ISIs in which statistical significance was found were not necessarily identical with those exhibiting the maximum modulation difference between the location of the conditioning stimulus (see below). Results of homotopic and heterotopic conditioning cutaneous stimulation on MEPs in APB and ADM from 14 subjects are summarized in Fig. 1.

For statistical analysis a three-factorial rmANOVA (site × muscle × ISI) was performed on the four curves. We found a significant effect of ISI ($F=2.07$; $P<0.01$), a significant site × muscle interaction ($F=10.59$; $P<0.01$), and site × muscle × ISI interaction ($F=3.96$; $P<0.001$). Site, muscle, and other interactions between factors were statistically insignificant.

To determine whether all ISIs were equally powerful in differentiating homotopic and heterotopic modulation

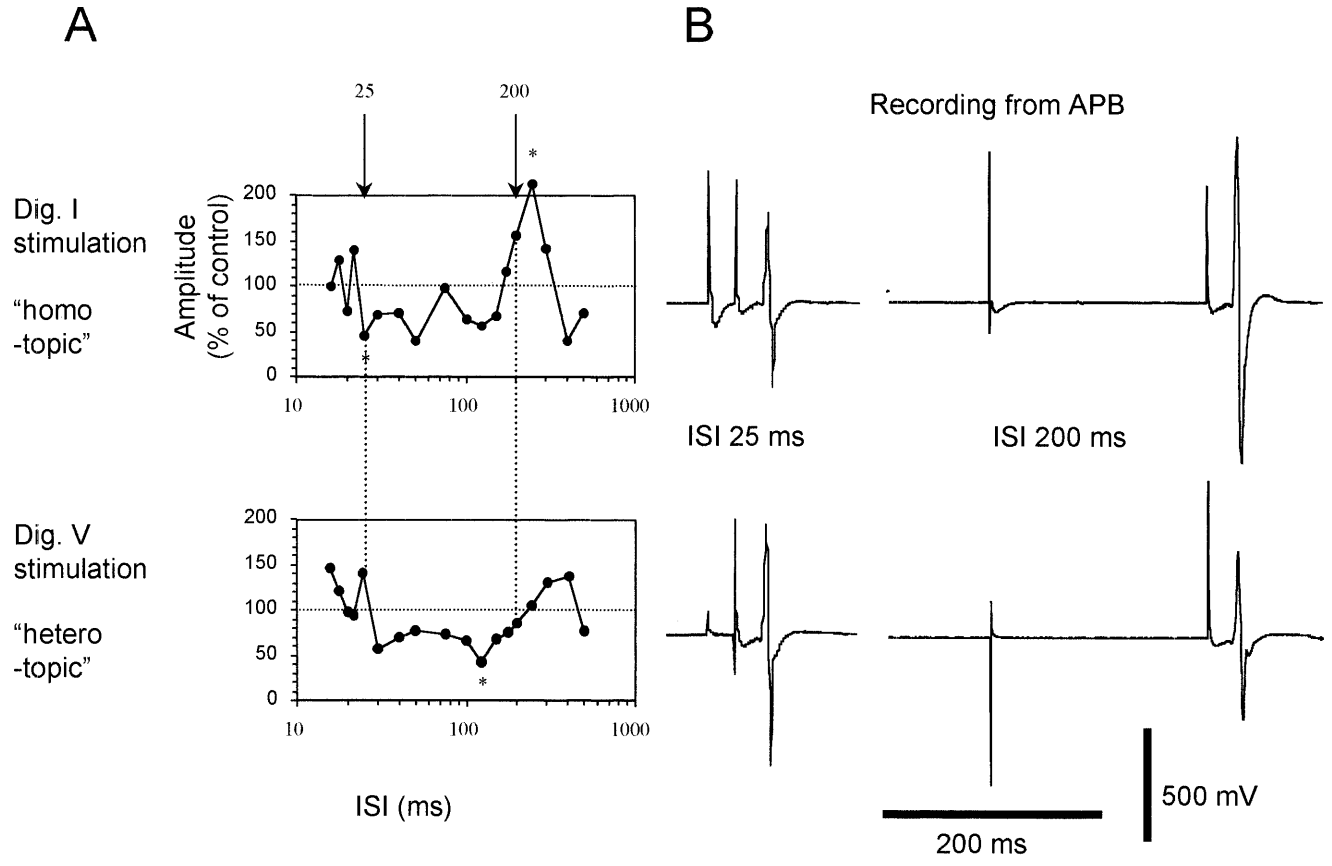


Fig. 2 **A** Time course of modulation of normalized MEP amplitude of APB by homotopic (radial side of dig. I) and heterotopic (ulnar side of dig. V) conditioning cutaneous stimulation at 200% perceptual threshold. Example of one subject. *Asterisks* values significantly different from the respective control (*t* test; $P<0.05$) **B** Effect of homotopic and heterotopic conditioning stimulation at 25 ms (*left*) and 200 ms (*right*) on normalized MEP-amplitude of APB. Average of 10 trials

of MEP amplitudes we calculated the difference between the means of homotopic and heterotopic stimulation as a function of ISI (Fig. 1B). The fact that neither a site nor a muscle effect was found in any of the statistical analyses allowed us to combine the homotopic, on one hand, and the heterotopic stimulation, on the other, for the two target muscles tested (Fig. 1B). Direct statistical comparison between homotopic and heterotopic stimulation using Student's *t* test revealed significant differences at ISIs of 25, 30, and 75–200 ms ($P<0.05$; Fig. 1C).

Somatotopically differential modulation of MEP size could potentially be generated at a cortical or a subcortical site. Therefore we employed transcranial electrical stimulation which is believed to excite the cortical output elements preferentially distal to the effect of intracortical interneuronal afferents (Rothwell 1997; Rothwell et al. 1991). Onset latencies of MEPs elicited by TES or TMS were analyzed in two subjects to investigate the possibility that TES, at the stimulus intensities used, produced a similar degree of indirect activation of pyramidal output elements as TMS. If this were the case, onset latencies should be similar in the two techniques. However, latencies were found to be significantly shorter (1.0 or 1.2 ms) when using TES (*t* test; $P<0.05$). We compared the effect of homotopic and heterotopic conditioning cutaneous afferent stimulation on normalized MEPs evoked in APB and ADM by TES or TMS at two different periods of short (25 and 30 ms) and long (150 and 200 ms) ISIs. These periods were selected on the basis of ISIs yielding the largest somatotopic effects in relaxed muscles according to Fig. 1C.

With TMS, results corresponded to the findings reported above for homotopic or heterotopic cutaneous conditioning at short or long ISIs. Homotopic stimulation produced an inhibition of TMS-evoked MEP amplitudes at short ISI and a facilitation at long ISI. With heterotopic stimulation the inhibition at short ISIs was less pronounced than with homotopic stimulation, and an inhibition was found at long ISIs. A similar differential pattern emerged with TES (Fig. 3). A three-way rmANOVA (type, latency, site) revealed a weak significant effect for site ($P<0.05$), a significant latency × site interaction ($P<0.001$), but no significant type × latency × site interaction. Thus a differential effect of the stimulation technique on latency × site interaction was not supported by this type of statistical analysis. It has been shown previously that the size of MEPs elicited by TMS can be facilitated by a puff of air applied approximately 200 ms before TMS to a skin region close to the muscle (Terao et al. 1995). This facilitation is specific to TMS and absent with TES, suggesting a cortical site. Based on these prior results, we hypothesized that in

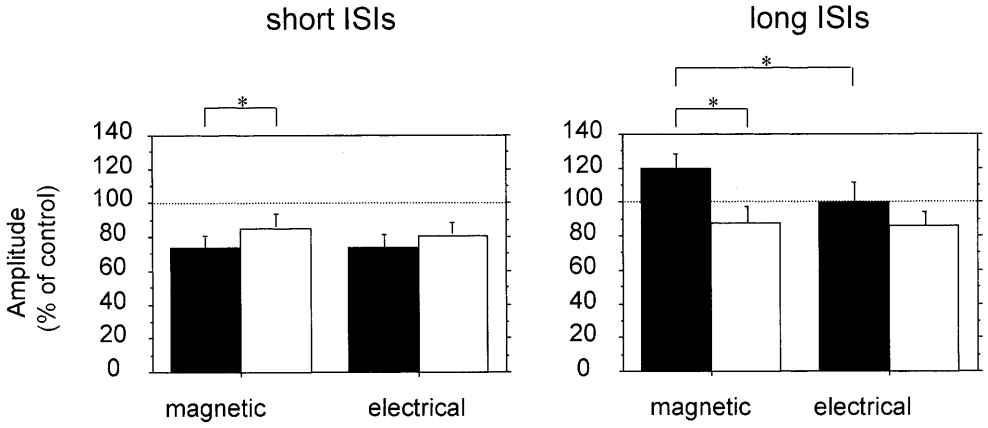


Fig. 3 Comparison of homotopic (*filled bars*) and heterotopic (*open bars*) modulation of MEPs of APB and ADM evoked by TES or TMS. Results from 7 subjects. Data indicate mean±SEM. Differences between homotopic and heterotopic conditioning stimulation are similar with TMS and TES at short ISIs (25 and 30 ms, *left*). At long ISIs (150 and 200 ms, *right*) homotopic facilitation is larger with TMS than with TES

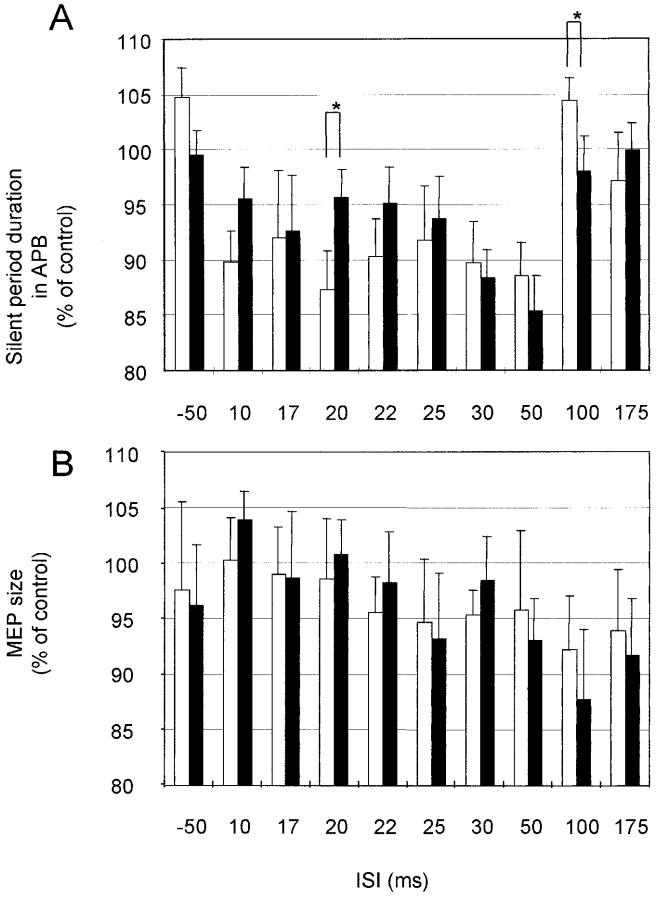


Fig. 4 A Time-dependence of somatotopic difference between homotopic (CS at dig. I, *open bars*), and heterotopic (CS at dig. V, *filled bars*) modulation of normalized SP duration in APB. ISI 20 ms. **B** Effect of homotopic or heterotopic (*symbols* as in **A**) stimulation on MEP size of APB. Means±SEM 10 subjects

our paradigm at long ISIs the homotopic facilitation differs with TES from that seen with TMS. Statistical testing, employing Student's *t* test confirmed more homotopic facilitation with TMS than with TES ($P<0.05$; Fig. 3). Statistical testing also confirmed differences between homotopic and heterotopic stimulation for TMS at both latencies ($P<0.05$, paired *t* test; Fig. 3) to be significant, in accordance with the findings presented above (Fig. 1C).

Observations in contracted target muscle (experiment 2)

In line with earlier findings (Hess et al. 1999), we found that a conditioning peripheral electric cutaneous stimulation induced a shortening of the SP in the APB. When the conditioning stimulus was applied to dig. I (homotopic stimulation), the SP shortening was elicited over a relatively broad range of ISIs extending from 10 to 50 ms (Fig. 4A). A shortening of the SP in the APB was also produced with heterotopic conditioning stimulation (CS to dig. V) but was generally less pronounced than with homotopic stimulation. The magnitude of the difference of SP shortening between homotopic and heterotopic stimulation depended on the ISI and was maximal at 20 ms. A two-way rmANOVA (site × ISI) revealed a significant effect of ISI ($F=2.21$; $P<0.05$), and a significant site × ISI interaction ($F=2.65$; $P<0.02$) suggesting an ISI-dependent difference between homotopic and heterotopic conditioning stimulation on SP shortening. Differences between homotopic and heterotopic stimulation were significant at 20 ms ($P<0.02$; *t* test) and 100 ms ($P<0.05$). With homotopic afferent stimulation SP duration was relatively shorter at 20 ms and relatively longer with 100 ms. Only the 20-ms interval showed a statistically significant shortening of the SP duration compared to the control condition. A similar analysis was carried out for MEP size (Fig. 4B). No significant main or interaction effects were found (rmANOVA).

The somatotopic gradient was explored in detail by varying the site of the CS on various digits. Silent-period shortening was most pronounced when the CS was delivered near the contracting target muscle and was gradually reduced with increasing distance between stimulation site and muscle (Fig. 5A). Conditioned silent period durations were significantly correlated with the rank order of the stimulated digit (APB: $y=0.85x-75.3$, $R^2=0.92$, $P<0.05$; ADM: $y=-1.79x+97.2$; $R^2=0.75$; $P<0.05$). MEP size (Fig. 5B) was not correlated with the rank order of the stimulated digit in any muscle.

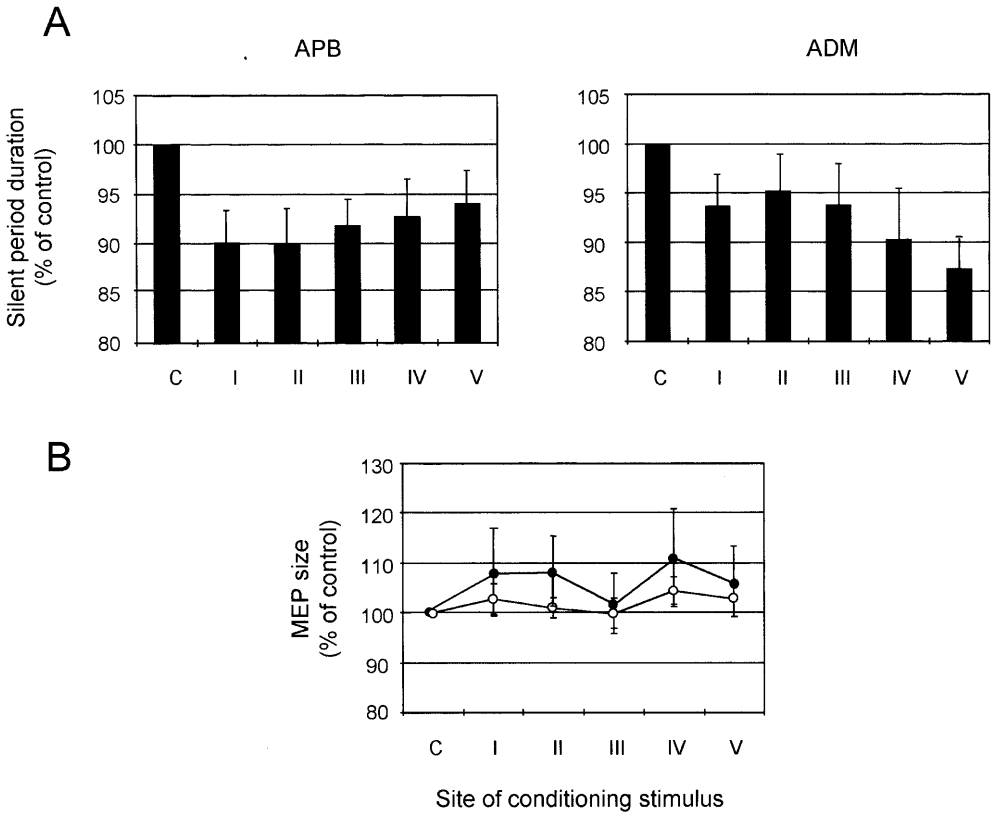
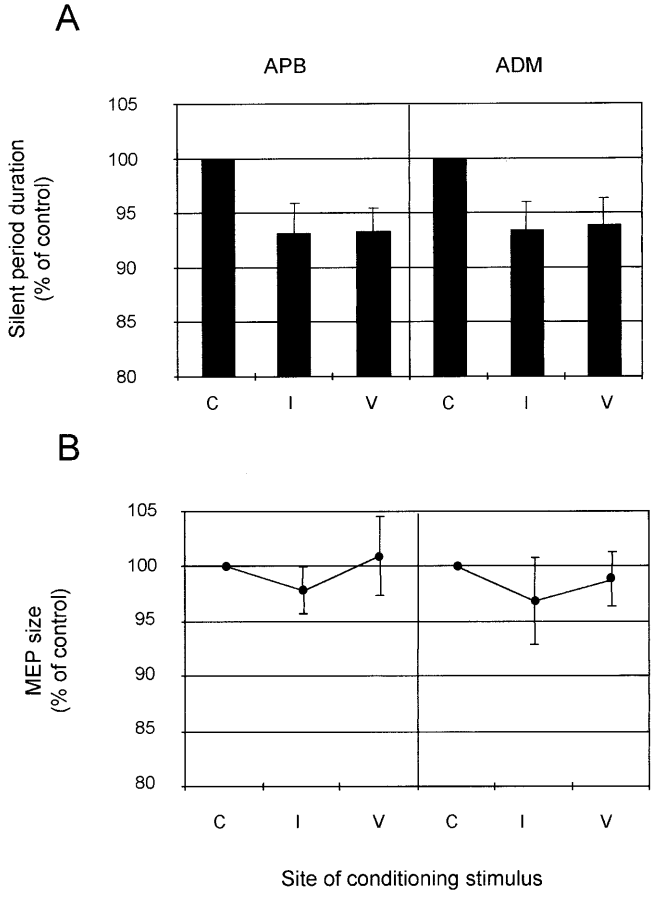


Fig. 5 **A** Somatotopic gradient of modulation of SP duration by afferent cutaneous stimulation of digit I to V. SP duration in the APB (*left*) or ADM (*right*) contracted at 15% of maximal voluntary force, normalized to the control condition (no cutaneous stimulation). **B** Absence of somatotopic gradient in mean normalized MEP size (*open circles* APB; *filled circles* ADM) in active target muscles when conditioned by stimulation of digit I to digit V. Data indicate mean±SEM from 11 subjects



When APB and ADM muscles were together isometrically contracted, SP duration was also shortened by a CS ($P<0.05$) but to a somewhat lesser degree. No somatotopic gradient was present between heterotopic and homotopic stimulation (Fig. 6). Using a two-way rmANOVA (site × muscle), no significant effects were found for either SP duration or MEP size (Fig. 6B).

Discussion

In this study we explored the level, timing, and task dependency of the somatotopic organization of cutaneomotor interaction in the human nervous system controlling the hand. Our results show that afferent modulation of motor potentials in the relaxed, but not in the active muscle, and of the TMS-evoked silent period in active muscles, depends on the location of the afferent stimulus on the hand and is similar for various intrinsic hand muscles. The degree of the somatotopic gradients depended both on the timing of the conditioning in relation to the test stimulus and on the motor task in which the muscle under study was involved.

Fig. 6 **A** Absence of somatopical gradient of SP modulation by homotopic or heterotopic stimulation with simultaneous contraction of APB and ADM. SP durations normalized to unconditioned control. **B** MEP size, normalized to unconditioned control, with homotopic or heterotopic stimulation. Data from 8 subjects. Means±SEM

Nature of somatosensory afferents

Conditioning stimulus intensities were intentionally kept low (200% or 300% of the perceptual threshold) to avoid contamination of signals from cutaneous afferents with those from joints or tendons. We are not aware of any systematically established threshold intensities for electrical stimulation of different types of afferents using microneurography and intraneural recordings in humans. Indirect evidence, however, can possibly be derived from a recent study by Priori et al. (1998) showing that stimulation of tendon afferents has a noticeable effect on voluntary EMG activity only at stimulus intensities near the pain threshold and therefore well above the intensities used in the present study. However, we cannot completely rule out the possibility that electric finger stimulation at weak intensities led to the activation of joint and tendon afferents exerting subliminal effects that were invisible in the experimental settings of Priori et al. (1998) but contributed to the phenomena in our study. However, even if this was the case, their effect is highly unlikely to be relevant at ISIs of less than about 35 ms because the afferents activated by stimulating tendons electrically likely belong to the slowly conducting group III afferents (Priori et al. 1998). Faster conducting tendon afferents are derived from Golgi tendon organs located at the musculotendinous junction which is located at a considerable distance from the conditioning stimulation sites.

Level of somatotopic sensorimotor integration

Short-latency effects

In relaxed hand muscles the modulation of MEP size by conditioning stimulation showed maximal somatotopic differences between homotopic and heterotopic stimulation at an ISI of 25–30 ms. This timing would be entirely consistent with, and indeed may be regarded as suggestive of, a cortical site of somatotopically organized sensorimotor integration. We were surprised therefore that such a view could not be substantiated by the experiments comparing the effects of TES and TMS on MEP size in differently conditioned muscles. It is generally agreed (Rothwell 1997; Rothwell et al. 1991) that TES at weak intensities activates pyramidal output cells more directly than TMS, which has a transynaptic mode of exciting pyramidal tract cells. Therefore the similar modulation of MEPs of conditioned intrinsic hand muscles with TES and TMS suggests a subcortical site of implementation of somatotopy. Because α-motoneurons targeting intrinsic hand muscles are predominantly activated monosynaptically (Porter and Lemon 1995), the site of somatotopic modulation is likely to be at a spinal level. Cutaneomotor integration in the spinal cord has been studied extensively in experimental animals, healthy volunteers, and patients with traumatic spinal cord transections. However, somototopical aspects have received comparatively little attention. Cutaneous stimulation of distal limb segments may produce complex patterns of muscle activation in the resting limb which result in a withdrawal movement resembling flexor reflexes obtained in the spinalized cat (Floeter et al. 1998; Roby-Brami and Bussel 1987; Shahani and Young 1971). The latency of human flexor reflexes is approx. 80–100 ms in human intrinsic hand muscles (Floeter et al. 1998). In our study the earliest somatotopic differences following cutaneous digital stimulation were seen at an ISI of 25 ms. When corrected for the MEP latency of about 20 ms, this event was visible at the periphery at approximately 45 ms and thus at a latency substantially shorter than the flexor reflex latencies. Therefore it seems unlikely that the spinal mechanisms underlying flexor reflexes are also operative in the production of the modulation of MEP amplitudes generating the somatotopic effects observed in the present experiments. Anatomical-physiological studies in experimental animals do not provide established models for how the somatotopic effects can be understood on the spinal level. These studies demonstrate that somatotopy of cutaneous afferents is preserved at a high degree in the dorsal horn of the spinal cord (Brown and Fuchs 1975; Koerber et al. 1993; Wilson et al. 1986). However, it is not known how this information is translated into modulation of the premotoneuronal and motoneuronal circuitry of the spinal cord.

The above considerations regarding a spinal site of somatotopical differences depend entirely on the view that TES and TMS excite the cortical output elements at different locations. To induce MEP amplitudes in the target muscles of sufficient size, stimulus intensities exceeding threshold intensities were used in the present study. At these stimulus intensities TES may have excited pyramidal output neurons not only directly, but also transynaptically, while the reverse may have been true for TMS. In the absence of direct recordings of corticospinal volleys we can only speculate as to whether this might explain the absence of a difference between the two stimulation techniques at short latencies, and whether this implies that the observed divergence between homotopical and heterotopical conditioning was indeed located cortically and not in the spinal cord. However, two points argue for a differential effect of the techniques even at suprathreshold intensities: At long ISIs, discussed below in more detail, the effects of conditioned TMS and TES were significantly different. If the mode of excitation had been the same for TES and TMS, one would have expected that the effects of a conditioning pulse on the effects of stimulation would have been the same for both stimulation techniques at all ISIs. Secondly, a more direct activation of cortical output elements by TES is also suggested by the fact that in two subjects, at comparable MEP size, onset latencies of MEPs were shorter by 1.0 or 1.2 ms following TES than following TMS.

With voluntary contraction of the target muscle we found, in agreement with a previous study (Hess et al. 1999), that the TMS-induced SP is shortened when TMS

is conditioned by peripheral stimulation. In contrast, the MEP size in contracted muscles was not significantly changed by conditioning stimulation. Evidence from multiple sources supports the view that the SP is a predominantly cortical phenomenon (Cantello et al. 1992; Fuhr et al. 1991; Inghilleri et al. 1993; Roick et al. 1993; Schnitzler and Benecke 1994). Although the exact neuronal basis of the SP is not known, analogy with inhibitory postsynaptic potentials in neocortical brain slices (McCormick 1992) as well as neuropharmacological observations (Werhahn et al. 1999) suggest that the SP represents activity of cortical inhibitory interneurons, acting upon $GABA_B$ receptors (Classen and Benecke 1995). Therefore modulation of SP is likely to reflect an interaction of tactile afferent signals with inhibitory circuits at a motorcortical level.

The degree to which the SP was shortened reflected the spatial relationship of the source of tactile information with the target muscle, or, in other words, exhibited a somatotopic gradient (Fig. 5). This observation corresponds to studies of cutaneomuscular reflexes demonstrating somatotopic organization of tactile afferent facilitation of voluntarily produced EMG activity at latencies comparable to the ones in the present study (Caccia et al. 1973; Deuschl et al. 1995). Since the cortical nature of the E2 component of cutaneomuscular reflexes is not generally accepted (see e.g., Maertens de Noordhout et al. 1992; Macefield et al. 1996; Palmer and Ashby 1992), our study provides unequivocal evidence of a somatotopic organization of short-latency tactile afferent modulation at the level of the motor cortex. Although afferents from the somatosensory cortex synapse with both excitatory and inhibitory cells in motor cortical layers II and III (Porter et al. 1990), the fact that MEP size in voluntarily contracted muscles was not significantly changed with conditioning stimulation suggests a privileged access of tactile information to inhibitory circuits.

Long-latency effects

In resting target muscles a second period of somatotopic differences between homotopic and heterotopical stimulation was observed at longer latencies of about 150–200 ms. The EMG events underlying this difference were inhibition of the heterotopically stimulated muscle and either less inhibition or, in some subjects, facilitation of the homotopically stimulated muscle. Following the arguments outlined above, the differential modulation of MEPs by TES and by TMS suggests that the somatotopy is partially spinal and likely has a cortical component. Studies on patients with complete spinal cord transections have been found cutaneomotor reflexes at several hundered milliseconds in the lower limb (Roby-Brami and Bussel 1987), suggesting that the spinal cord is capable of producing complex muscular activation patterns at long latencies. Thus the latencies of the EMG events corresponding to the late period of somatotopy appear compatible with a partial spinal origin. On the other hand, the experiment comparing cutaneous afferent modulation of TES- and TMS-evoked MEPs revealed an additional facilitation in the homotopically stimulated muscle only when TMS was used. This finding confirms results obtained in the recent study by Terao et al. (1995), who showed that the size of MEPs elicited by TMS could be facilitated by a puff of air applied approximately 200 ms before TMS to a skin region close to the muscle. Similar to our observation, air stimuli had no facilitative effect on MEPs evoked by TES, suggesting that the effect observed with TMS was produced at a cortical level.

With active contraction of a target muscle, homotopic and heterotopic conditioning stimulation had a differential effect on SP duration at an ISI of 100 ms. Interestingly, the SP duration was neither shortened nor lengthened significantly at the different conditioning sites compared to the control. This finding suggests that somatotopic patterns of modulation may exist without profound inhibitory or facilitative effects at the level of single muscles. Under some circumstances the behavioral effect of a cutaneous stimulus may more likely be determined by the pattern of modulation in a set of synergistic muscles than by net excitation or inhibition of single muscles.

Route of afferent signals

Hess et al. (1999) found that the SP is maximally shortened when the CS at the wrist is delivered at a short interval before TMS, but that the precise timing of the peripheral stimulation is not critical to producing any effect on the SP duration. In our study the difference between the effects of homotopical and heterotopical stimulation was maximal and statistically significant at an ISI of 20 ms. As is argued below, this timing is consistent with modulation of neuronal elements involved in the generation of the SP within the motor cortex by a fast afferent volley via rapidly conducting afferents relayed in the somatosensory cortex. The time of arrival at the somatosensory cortex of a cutaneous afferent signal from a digit can be estimated from the latency of the N22 component of the sensory evoked potential (Fuhr and Friedli 1987; Macefield and Burke 1991). In our study the N22 averaged to 22.3 ms. Pathways from somatosensory cortices to pyramidal tract cells, the motor cortical output cells located in layer V, are either monosynaptic, targeting directly layer V pyramidal tract neurons (Porter 1996) or oligosynaptic, involving an intermediate relay in MI cortical layers II/III (Kaneko et al. 1994b). In the cat, latencies between area 2 stimulation and monosynaptic responses in layer II/III of the motor cortex can be as short as 1.2 ms (Kaneko et al. 1994a; Zarzecki 1989). Because of the longer distance a conservative estimate for the same route in humans would be 2–3 ms. This would imply that the earliest signal taking a passage through the somatosensory cortex would arrive at the primary motor cortex approximately 25 ms after the peripheral stimulus. The latency of TMS-induced suppression of voluntary EMG activity is approximately 3–8 ms longer than the

latency of evoked muscle potentials (Davey et al. 1994). Although the initial part of the SP may to some extent be spinal (Fuhr et al. 1991), at least a portion of even its initial part is likely to be generated cortically (Davey et al. 1994; see also Schnitzler and Benecke 1994). The 3- to 8-ms longer latency of the SP therefore likely reflects the minimum intracortical processing time for interneurons to initiate a cortical inhibition. Afferent signals from the somatosensory cortex could be timed to modulate motor cortical processes involved in the initiation of the SP if the magnetic stimulation follows the peripheral stimulation by a maximum of 17–22 ms (25 minus 8 to 25 minus 3) which corresponds excellently with the observation that the largest somatotopic effects were observed at an ISI of 20 ms.

A second period of somatotopic modulation of SP duration was noted at an ISI of 100 ms. This may suggest that cutaneous afferent information relevant for the generation of somatotopic modulation can also reach the motor cortex via a less direct, slower conducting, likely polysynaptic route.

Task dependence of somatotopic sensorimotor integration

With the contraction of a single target muscle the shortening of SP reflected the site of the CS to a surprising degree (Fig. 5). In principle, this finding and the results by Caccia et al. (1973), Deuschl et al. (1995), and Meinck et al. (1987) would support a model of a hardwired and tight somatotopic organization of motorcortical input-output relationship as suggested by the first detailed investigations of sensorimotor integration in MI (Asanuma and Rosén 1972a, 1972b; Rosén and Asanuma 1972). These authors have reported that in the monkey each efferent column in MI appeared to receive sensory information from a portion of a limb in close anatomical relation to the muscle to which it projects and, even more specifically, from that side of the finger or hand which is in the direction of a movement produced by intracortical microstimulation. However, such a degree of hardwired input-output relationship has not been confirmed in subsequent studies in experimental animals. Cutaneous receptive fields of output neurons in MI were not found to be correlated with the direction of movements evoked by stimulation of output neurons in the study by Strick and Preston (1983). In the cat, evidence was presented for a spatially specific sensorimotor input-output link to the degree that a single sensory column in area 2 can project to a single motor column in area 4, but that intracortical microstimulation of area 2 more frequently produces responses extended broadly over the entire area 4 (Caria et al. 1997). Other studies (Zarzecki 1989, 1991) suggest that specificity of input-output-relationships, albeit detectable at a single motoneuron level, are not present at a column level because neighboring neurons projecting to the same targets were found to receive afferent information from various sources, and the same afferent sources modulated the activity of neurons projecting to different targets. Thus despite its immediate and intuitive appeal the original model of a tight and hardwired somatotopic input-output relationship in MI with observable equivalents on a relatively broad behavioral scale is likely to be too simplistic.

This reasoning gains support in our findings that the degree of SP shortening is similar, but that the spatial gradient of afferent modulation of SP duration is lost if the motor task involves attention to simultaneous contraction of two distant muscles rather than contraction of one target muscle (Fig. 6). This suggests that the spatial gradient at which tactile afferent signals can modulate inhibitory interneurons is subject to modulation. A task-dependent modulation of cortical motor output circuits has been shown in humans by testing the excitability of corticospinal motoneurons (Datta et al. 1989; Flament et al. 1993), or the size of presumably cortical components of cutaneomuscular reflexes (Datta et al. 1989; Evans et al. 1989), but the mechanisms by which this modulation is achieved remain unknown. The present results now suggest that one mechanism by which the cortex can control the implementation of certain motor tasks is changing the gain and gradient of cutaneous afferent modulation of motor cortical inhibition. Such a mechanism could be important in manipulative motor tasks when attention is focused on the action about a single body part. Under these circumstances the effect of tactile afferent information on intracortical inhibition is greater when the source of the information is close to the active muscle. In situations in which activity involves many muscles, such as in a power grip, such a somatotopic gradient is not needed and may even be disturbing. The prominent role of inhibition indicated by the present findings is in accordance with experiments in the monkey motor cortex suggesting strongly task-dependent modulation of GABAergic inhibition during voluntary motor behavior (Matsumura et al. 1992).

The type of cutaneous stimulation and the type of the motor behavior (relaxed muscles, isometrically contracted muscles) tested in the presented study represent conditions deviating from natural movements in many respects. The precise behavioral significance of our findings will have to be addressed in future studies; however, it is conceivable that the task-dependent spatial distribution of cutaneous modulation in synergistic muscles is a major determinant in the control of natural movements, for example, in tactile exploration. Any disturbance in that organization is likely to result in disturbances of motor behavior. Indeed, some neurological disorders, such as certain types of focal dystonias, can be viewed as examples of a disorganized input-output link within the central nervous system (Hallett 1995). In line with this hypothesis, it is important to note that disturbance of somatotopic representation of afferent cutaneous information in the somatosensory cortex per se does not necessarily lead to functional motor impairment and may even be associated with superior perceptuomotor abilities

(Sterr et al. 1998a, 1998b). The task-dependency of involuntary contractions in dystonia and the frequent observation that cutaneous stimulation near the involved muscles eases their dystonic spasms suggest that studies investigating the somatotopy of cutaneomotor integration in dystonia will reveal important insights into the pathophysiology of this disease.

Acknowledgements The authors thank M. Johnson for proofreading the manuscript. This study was supported by DFG grant Cl 95/2-2 and Cl 95/3-1.

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