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Effects of electric and magnetic transcranial stimulation on long latency reflexes

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Summary. The interaction of transcranial electric and magnetic brain stimulation with electrically elicited short- and long latency reflexes (LLR) of hand and forearm flexor muscles has been investigated in normal subjects. In the first paradigm, the motor potential evoked in thenar muscles by transcranial stimulation was conditioned by median nerve stimulation at various conditioning-test intervals. At short intervals (electric: 5–12.5 ms, magnetic: 0–7.5 ms) facilitation occurred that corresponded to the H-reflex and at longer intervals (electric: 25–40 ms, magnetic: 22.5–35 ms) there was a facilitation corresponding to the LLR. Electric and magnetic stimulation resulted in a similar degree of facilitation. A second paradigm investigated the facilitation of the forearm flexor H-reflex by a cutaneo-muscular LLR elicited by radial superficial nerve stimulation and transcranial stimulation used separately or together. When electric and magnetic brain stimulation were compared, magnetic brain stimulation was followed by significant extrafacilitation but electric stimulation was not. This result favours an interaction between the afferent volley eliciting the LLR and transcranial magnetic stimulation most likely at supraspinal level.

Key words: Long latency reflexes – Transcranial stimulation – Physiology – Human

Introduction

Long latency reflexes (LLR) of human hand- and forearm muscles can be elicited in voluntary contracted muscles by various stimuli such as muscle stretch (Marsden et al. 1973), electrical stimulation of pure muscle afferents (Deuschl et al. 1985), mixed nerves (Upton et al. 1971; Conrad and Aschoff 1977; Meinck et al. 1987) or pure cutaneous afferents (Caccia et al. 1973; Jenner and Stephens 1982; Deuschl et al. 1985). At least for the muscles acting at the wrist and fingers, evidence obtained in animal experiments (Conrad and Meyer-Lohmann 1980; Cheney and Fetz 1984) and in man (Marsden et al. 1973, 1983; Noth et al. 1985; Abbruzzese et al. 1985; Deuschl et al. 1988b) indicates that long latency reflexes are conducted along a transcortical loop.

Using the recently developed techniques of transcranial electrical (Merton and Morton 1980; Day et al. 1987a; Rothwell et al. 1987; Rossini et al. 1987a, b; Benecke et al. 1988) and magnetic (Barker et al. 1985; Hess et al. 1987) stimulation of the motor cortex, we have studied a possible interaction between transcranial stimulation and short or long latency reflexes of muscles acting at the fingers or wrist in human subjects. We used two experimental paradigms. In the first, the potentials evoked in the thenar muscles by transcranial stimulation were used as the test stimulus to study the facilitation exerted by a median nerve shock at the wrist. In the second, the Hoffmann-reflex in relaxed finger flexors was used as a test reflex, with two conditioning stimuli: transcranial stimulation, subthreshold for eliciting an evoked motor response in finger flexors, and stimulation of the radial superficial nerve (rsn) to evoke an LLR in finger flexors.

The results provide evidence that short and long latency reflexes are both facilitated by transcranial stimulation. However, long latency reflexes receive additional facilitation from magnetic but not from electric transcranial stimulation. Part of the results have already been presented (Deuschl et al. 1988a).

Methods and subjects

Subjects

The subjects (16 males, 5 females, age: 22–65 years) were hospital and laboratory personnel. They took part in a total of 35 experi-

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mental sessions. The experimental procedures were approved by the local ethical committee and the subjects gave their informed consent. Each subject received no more than 200 shocks per day. During the experiments the subjects were seated comfortably in a reclining chair. All the experiments were performed at the left arm.

Reflexes

Thenar muscles: reflexes in contracting finger muscles were elicted by electrical stimulation of the median nerve at the wrist (for details see Deuschl et al. 1985). Stimulus strength was set to the threshold for motor fibres. The electromyographic response in thenar muscles was recorded with a surface electrode in belly-tendon fashion. The signal was filtered (1.5–3000 Hz), rectified and averaged (128–512 sweeps).

Finger and wrist flexors: muscle activity was recorded over the muscle belly of the flexor group. The electrode position was optimized to obtain the largest amplitudes of the EMG responses during voluntary activation of hand and finger flexors. To elicit long latency reflexes in contracted flexors, the radial superficial nerve was stimulated at the wrist with surface electrodes placed 2 cm apart over the course of the nerve. Stimulus strength was set at 2–3 × perception threshold. The EMG signal was filtered, rectified and averaged (see above). To elicit the Hoffmann-reflex (H-reflex) the median nerve in the cubital fossa was stimulated at or just below threshold intensity for motor fibres. Relaxation of the flexors was verified by EMG monitoring.

Transcranial stimulation

Electrical stimulation of the motor cortex was performed according to the method of Merton and Morton (1980). A capacitive discharge with 20–50% of 750 volts with a time constant of 50 μs (Digitimer D 180) was applied through needle or surface electrodes. The anode was placed over the hand area of the motor cortex (at a point 2 cm anterior and 7 cm lateral to the vertex). The cathode was placed at the vertex (Rothwell et al. 1987).

Magnetic stimulation of the brain was performed with a commercial apparatus (Novametrix, Magstim 200) with a maximum magnetic field of 1,5 tesla. The coil was centered over the vertex and kept in a fixed position (Hess et al. 1987). The intensity of stimulation was set to between 30 and 90% of the maximum discharge. Electrical and magnetic stimulation was performed with the subjects at rest in order to minimize the variability of the responses.

Experimental procedures

1. Conditioning of transcranial shocks by median nerve stimulation. (5 subjects: 4 subjects tested with both electrical and magnetic stimulation). The muscle evoked potentials (MEPs) recorded in the thenar muscles after transcranial stimulation were compared, with and without conditioning stimulation of the median nerve, at different conditioning-test intervals. In five subjects, the test stimulus was applied by electrical stimulation and in five others by magnetic stimulation.

The control-MEP was set to 0.3–1.3 mV (peak-to-peak amplitude) corresponding to 5–10% of the maximum-MEP determined for each subject. The latency of the MEP was 20–22 ms (mean ± SD: 20.9 ± 0.9 ms) for electrical, and 22–25 ms (23.5 ± 1.2 ms) for magnetic brain stimulation. The median nerve shock was delivered before the cortical stimulus. The delay (from −5 to 55 ms) was increased stepwise by 2.5 ms or 5 ms. For each conditioning-test interval transcranial shocks were given randomly with or without median nerve shocks and 4–6 conditioned and unconditioned responses were compared. Peak-to-peak amplitudes were measured and the differences between conditioned and control-MEPs were assessed using the two-tailed Students t-test.

2. Conditioning of forearm flexor H-reflexes by radial superficial nerve stimulation. (12 subjects). H-reflexes were elicited in relaxed forearm flexors. In four subjects unconditioned and conditioned responses to stimulation of the radial superficial nerve (rectangular pulses, pulse width: 200 μs, 2–3 times perception threshold) were compared at varying conditioning-test intervals in steps of 2.5 ms for the conditioning-test period, which ranged from 20 and 60 ms. At each interval 10 conditioned and 10 unconditioned H-reflexes were elicited and peak-to-peak amplitudes were compared by the two-tailed t-test. In the remaining eight subjects, the conditioning of the H-reflex was tested at one fixed conditioning-test interval, calculated as the difference of the LLR peak latency and the H-reflex latency (Deuschl et al. 1989). The size of the control H-reflex was adjusted to about 10% of M_{max} corresponding to 25% of H_{max}. This was 0.5–2.9 mV. The size of M_{max} ranged between 5 and 19 mV with a mean of 11 mV ± 3.7 mV. H_{max} had a mean amplitude of 3.9 ± 1.6 mV with a range between 2.5 and 8 mV.

3. Conditioning of forearm flexor H-reflexes by radial superficial nerve and transcranial shocks. (11 subjects: 3 with both, electric and magnetic cortical shocks). H-reflexes of the forearm flexors were used as test reflexes. They were conditioned either by radial superficial nerve stimulation, by cortical stimulation or by both stimuli together.

Each of these four conditions was tested randomly 10–16 times. Peak-to-peak amplitudes of the H-reflexes were measured and analysed statistically offline (see below). The timing of the different stimuli was determined as follows. The flexor H-reflex was elicited, its latency was determined and the stimulus strength was adjusted to obtain a 25% response of H_{max} (see: methods 2). In the next step the LLR in the contracted forearm flexors was elicited by stimulation of the radial superficial nerve and the peak value of the LLR was determined for each subject. Then the latency of the MEP elicited by transcranial stimulation in the forearm flexors was measured.

The conditioning time intervals were choosen with respect to the radial superficial nerve stimulus. The delay in giving the cortical stimulus was calculated by subtracting the latency of the MEP from the peak latency of the LLR; the delay of the median nerve stimulus at the elbow was calculated by subtracting the H-reflex latency from the peak latency of the LLR (Deuschl et al. 1989). All the excitatory effects thus converged at the same time.

The mean and standard error of the mean (SEM) were determined for each 10–16 trials of the four conditions. The mean of each test condition (condition 2–4) was normalized to the mean of the control H-reflex. The corresponding standard errors of the mean were calculated according to the propagation of errors.

The goal of statistical analysis was to compare the mean H-reflex size when radial superficial nerve and cortex were stimulated simultaneously with the size of an H-reflex which is expected by arithmetic summation of the mean control H-reflex plus the mean conditioning effects of radial superficial nerve shocks and cortical shocks separately. The difference of these measured and calculated mean values gives a measure of the extrafacilitation exerted when both stimuli are given together. The measured and calculated mean H-reflexes with their corresponding standard errors of the mean were assessed with a two-tailed Students t-test.

Results

Test-MEP's conditioned by median nerve stimulation

The MEP in thenar muscles at rest after transcranial stimulation, showed two periods of facilitation: the first corresponded to the time of the H-reflex and the second to that of the LLR. In two subjects, there was a period of inhibition between the two reflexes.

In the five subjects in whom electrical transcranial

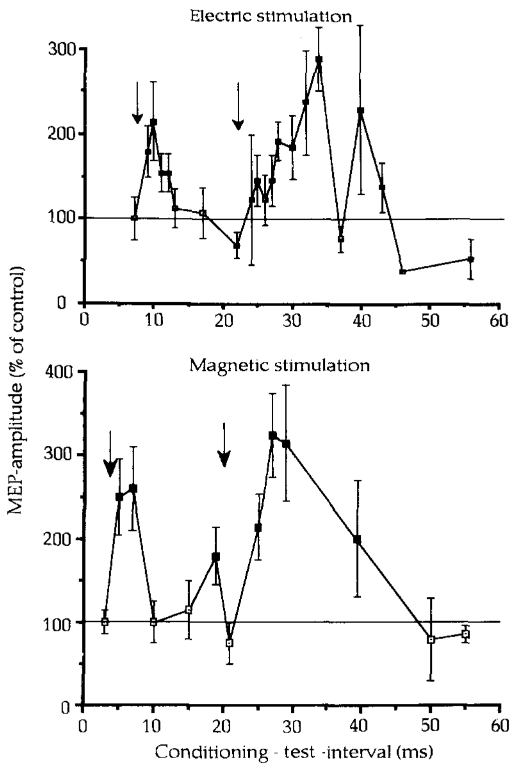

Fig. 1. Time course of the thenar MEP-amplitude after electric or magnetic brain stimulation conditioned by a median nerve shock in the same subject. The median nerve shock was given at time zero. Mean and SEM are shown for each conditioning-test interval as the percentage of control MEP. The arrows indicate the calculated onset latencies of the H-reflex and LLR. Filled quadrangles indicate significant differences ($p < 0.05$). Two periods of facilitation corresponding to H-reflex and LLR, can be seen with both kinds of brain stimulation

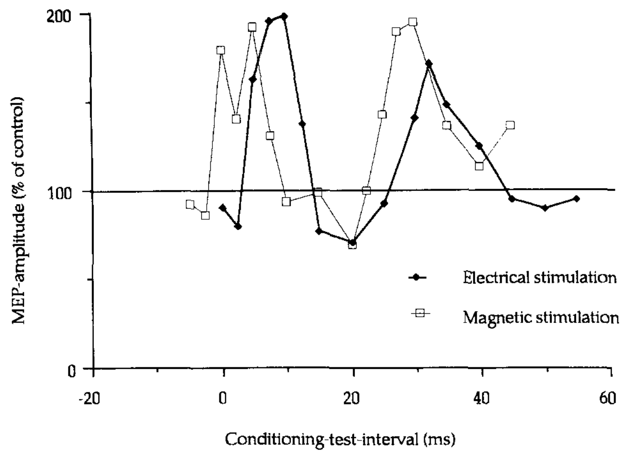

Fig. 2. Time course of the thenar MEP-amplitude following electric or magnetic stimulation (mean values of four subjects). Each point has been calculated from the mean values at the appropriate latency in the four subjects. Facilitation can be seen during the time period of the H-reflex and LLR

stimulation was applied a significant facilitation ($p < 0.05$) was seen in the time period between 5 und 12.5 ms. Four of the five subjects had a second period of significant facilitation between 25 ms and 40 ms. Moreover, in two subjects there was a significant inhibition of the test MEP between both facilitatory periods. The first period of MEP facilitation corresponds to the LLR. Figure 1 displays the MEP conditioning curve of a representative subject exhibiting the two periods of facilitation. The arrows indicate the onset of the H-reflex and LLR as calculated by subtracting the MEP latency from the appropriate values of routine reflex testing with contracting thenar muscles.

Magnetic transcranial stimulation in four subjects showed basically the same result. In all the four subjects, a significant facilitation of the MEP was found between 2.5 and 7.5 ms (conditioning-test interval). In three of the four subjects a second facilitation occurred between 22.5 and 35 ms. Two subjects had a significant inhibition between both facilitatory periods. Figure 1 gives the data of a representative subject.

Figure 2 shows the averaged data after electrical and magnetic stimulation in four subjects. Two periods of facilitation are again clearly discernible. The amount of facilitation produced by the median nerve shock after electric or magnetic brain stimulation is virtually identical. The most pronounced difference between the two modes of stimulation is the latency shift between the facilitation periods with shorter conditioning-test intervals for magnetic stimulation. This finding reflects the longer time required for magnetic excitation to reach the motoneurones.

The second aim of the study was to clarify whether the amount of facilitation was different for the H-reflex and the LLR. For a number of possible reasons (see discussion) the present experiments gave no hint of such a selective effect. Further attempts concentrated on quantifying this facilitation more exactly. For this purpose the experimental approach was changed.

LLR of forearm flexors

The second paradigm was designed to investigate the facilitatory action of transcranial stimulation on the LLR of forearm flexors. As little is known about the electrically elicited LLR of forearm flexors, experiments were undertaken to display the pattern of these reflexes in contracting and relaxed muscles. The reflex responses that follow median nerve or radial superficial nerve stimulation are not limited to the thenar muscles but they exhibit a more widespread distribution.

Figure 3 shows a typical example of the reflex responses elicited after median nerve stimulation at threshold, in seven hand and arm muscles in the co-contracting arm and hand muscles. Although the H-reflex and LLR are clearly discernible in several hand and arm muscles, biceps and triceps muscles do not exhibit significant reflex responses. After radial superficial nerve stimulation (Fig. 3) the H-reflex is absent and the LLR is discernible in the forearm flexors and in the hand muscles. The LLR of forearm flexors, obtained in response to stimulation of the radial superficial nerve, was evaluated in 12 subjects. Its onset latency was 53 ms ± 4.3 ms and its peak latency was 56 ms ± 5.2.

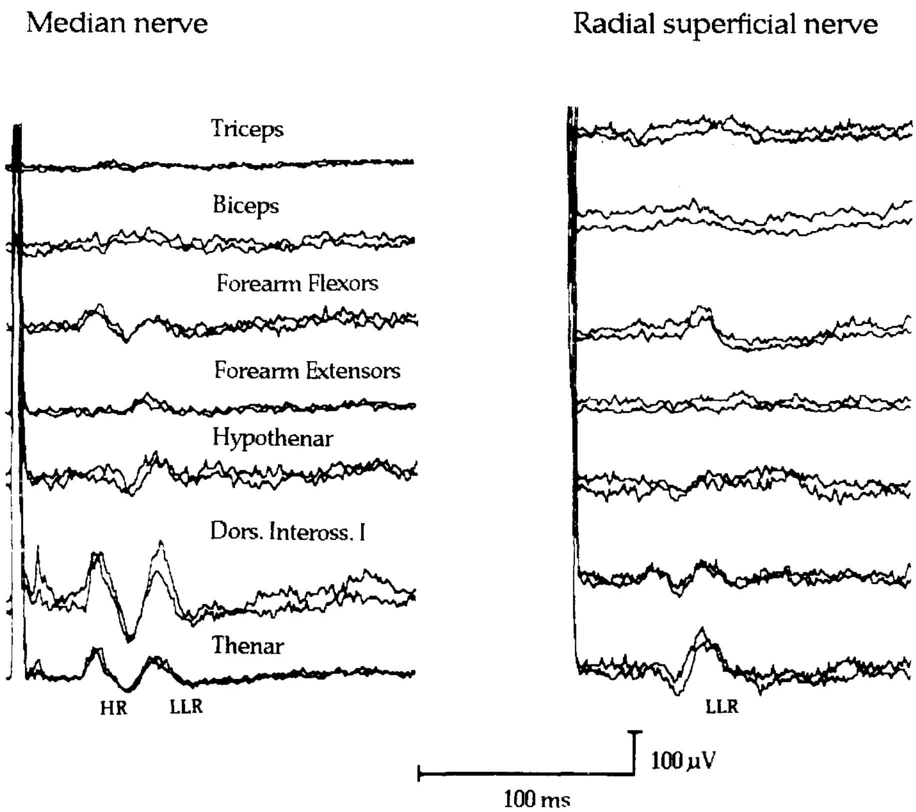

Fig. 3. Reflex pattern, in cocontracting hand and arm muscles, recorded simultaneously for median nerve or radial superficial nerve stimulation (each line is the average of 512 sweeps). After median nerve stimulation (see stimulus-artefact) a small M-wave followed by two reflexes can be seen in thenar and dorsal interosseus muscles. A homonym H-reflex is seen in the thenar and a heteronym H-reflex in the dorsal interosseus and forearm flexors. The LLR has a more widespread distribution in flexor and extensor muscles of the hand and arm. After stimulation of radial superficial nerve an LLR can be seen in the hand muscles and in the forearm flexors

However, in the relaxed forearm flexors, excitatory or inhibitory effects cannot be seen unless the level of excitability of the motoneurone pool is tested with an appropriate method. For this purpose the H-reflex technique was applied. The time course of the facilitation of the forearm flexor muscles following a radial superficial nerve shock was investigated in four subjects. Significant facilitation of the H-reflex was found at conditioning-test intervals of 30 to 80 ms with a maximum between 40 and 60 ms. The maximal facilitation for each subject varied between 165% and 270% of the test response. Figure 4 shows a typical example with significant facilitation between 42 ms and 57 ms and Fig. 5 shows averaged data of 4 subjects.

The onset and peak latencies of the LLR elicited in the contracting forearm flexors were compared with the onset and peak latencies of the facilitation period as revealed by H-reflex testing. The mean difference was 1.2 ms for the onset latency, and 8 ms for the peak latency.

We conclude that the H-reflex technique will demonstrate a facilitation of the forearm flexor motoneurones even in relaxed muscles. As the time course of this facilitation is the same as for LLR of contracting forearm

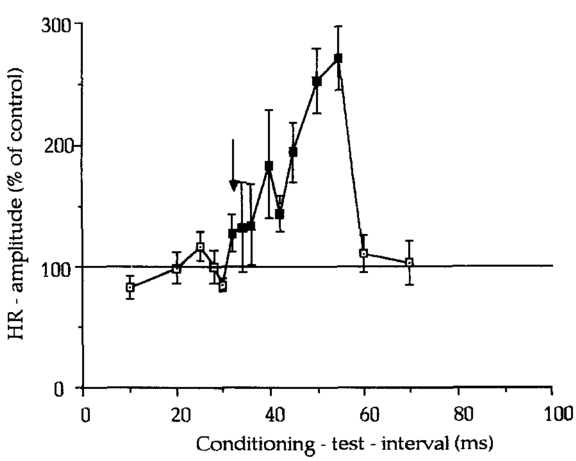

Fig. 4. Time course of facilitation of wrist-flexor H-reflex after radial superficial nerve stimulation. Black quadrangles indicate significant facilitation ($p < 0.05$). The arrow indicates the calculated beginning of the LLR in the contracting muscle

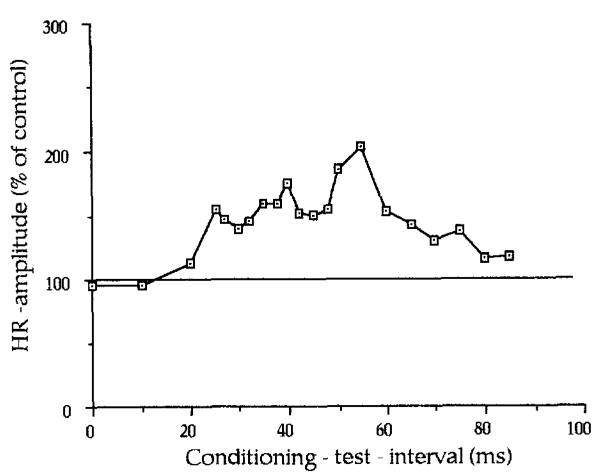

Fig. 5. Time course of facilitation of wrist flexor H-reflex after radial superficial nerve stimulation (averaged data of four subjects)

flexors, the excitations at rest and during contraction are presumably the same. The reflex excitation that follows a radial superficial nerve shock must be a cutaneo-muscular long latency reflex and the influence of cortical stimulation on this reflex was tested in a further series of experiments.

Conditioning of the forearm flexor H-reflex by cortical and radial superficial nerve stimulation

The H-reflex of relaxed forearm flexors was used as the test reflex. Stimulation of the radial superficial nerve was used to elicit an LLR and transcranial stimuli were given as conditioning stimuli. The conditioning-test intervals for the three stimuli were adjusted to the peak value of the LLR in each subject (see methods). The mean values of these intervals are displayed in Table 1.

Seven subjects were investigated with electric transcranial stimulation. Significant facilitation (t-test, $p < 0.05$) was seen after radial superficial nerve and transcranial stimulation in four of the seven subjects (see Table 2 for mean values). In one subject, cortical stimulation and in another radial superficial nerve stimulation showed a slight but not statistically significant facilitation. The extrafacilitation defined as the difference between the measured value for double-facilitation and the expected value by arithmetic summation of the facilitation exerted by each stimulus separately (see methods) ranged between −39% and 45% (mean 9%). In none of the subjects was the extrafacilitation of statistical significance.

Seven subjects were investigated with magnetic transcranial stimulation including three of the subjects which were investigated with electrical stimulation. The facilitation exerted by each of the stimuli separately was significant (t-test, $p < 0.05$) in six of seven subjects. Figure 6 shows a representative example. However, in contrast to transcranial electrical stimulation, in all but one of the investigated subjects the magnetic extrafacilitation was much larger (Fig. 7). This extrafacilitation was significant in four of the seven subjects (t-test, $p < 0.05$). The three subjects studied with both, electrical and magnetic stimulation all showed a significant extra-facilitation after

Table 1. Mean and standard deviations (SD) for the delays of cortex stimulation and median nerve stimulation with respect to the radial superficial nerve (rsn)-stimulus

	Conditioning-test interval between rsn-stimulus and median nerve stimulus	Conditioning-test interval between rsn-stimulus and transcranial shock
Electrical cortex stimulation ($n = 7$ subjects)	43.5 ± 4.7 ms	46.7 ± 4.8 ms
Magnetic cortex stimulation ($n = 7$ subjects)	43.8 ± 2.8 ms	44.2 ± 4.7 ms

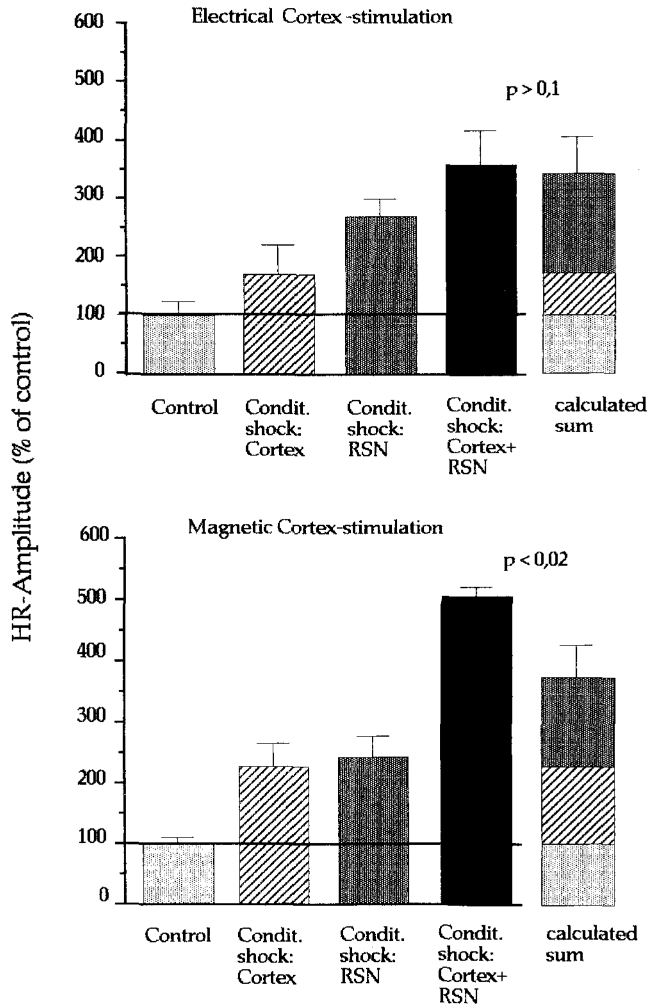

Fig. 6. Facilitation of wrist flexor-H-reflex conditioned by electric or magnetic brain stimulation respectively and radial superficial nerve (RSN) stimulation in one subject. The column at the right displays the expected facilitation for stimulation of the brain and RSN as revealed from both separate stimulations (see methods). The *p*-values indicate the result of t-test when comparing the measured facilitation by double stimulation and the expected value. After electric stimulation there was no significant difference but significant differences were produced by magnetic brain stimulation

magnetic stimulation (the first three bars of Fig. 7 represent these subjects). A comparison of the extrafacilitation in electric versus magnetic brain stimulation shows a significant difference ($p < 0.025$, Mann-Whitney). The variance of the extrafacilitation did not differ significantly.

Finally, we examined whether the difference in the extrafacilitation exerted by electric or magnetic transcranial stimulation could be due to methodological differences like different amplitudes of the test H-reflex or different percentages of facilitation exerted by the conditioning stimuli. The timing of conditioning stimuli was the same (see Table 1) except for the shorter conditioning-test interval needed for magnetic stimulation (because of the longer central conduction of magnetic brain stimulation). The amplitude of the test H-reflex in % of H_{max} (Table 2) and the amount of facilitation exerted by

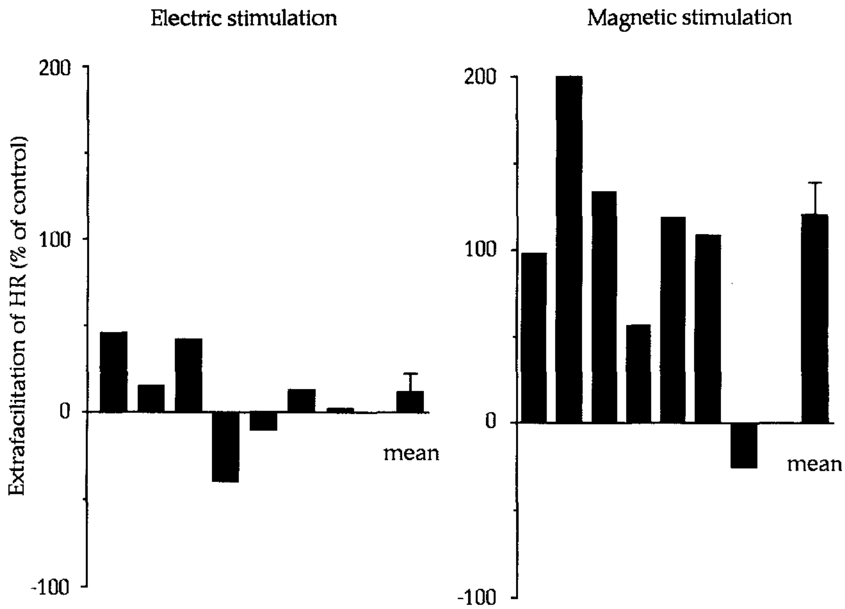

Fig. 7. Difference between measured and expected facilitation (extrafacilitation) after electric stimulation and magnetic stimulation in the subjects (see also Fig. 6). Except in one case, the difference is much larger with magnetic stimulation and is significant in four subjects

radial superficial nerve stimulation or transcranial stimulation (Table 3) were similar in magnetic and electric transcranial stimulation. All these parameters failed to reach significance on t-test ($p > 0.1$). Methodological differences between the two series of experiments are thus unlikely to account for the divergence of extrafacilitation.

Table 2. Mean and standard deviations of the amplitude of the test H-reflex in forearm flexors in the experiments with electric or magnetic transcranial stimulation

	Amplitude of the test H-reflex	
	Absolute (mV)	% of H_{max}
Electrical cortex stimulation ($n = 7$ subjects)	0.69 ± 0.34	29.2 ± 7.9
Magnetic cortex stimulation ($n = 7$ subjects)	0.95 ± 0.86	29.0 ± 16.5

Discussion

The results demonstrate an interaction within the CNS between the afferent volley of peripheral nerves and the descending volleys elicited by transcranial stimulation of the motor cortex. To demonstrate this interaction we used two different paradigms.

In the first, transcranial stimulation was used to test the facilitatory influence exerted by a median nerve volley. Two periods of facilitation were demonstrated and the first of these corresponded to the H-reflex. This facilitation is obviously related to the spatial summation of the excitatory effect of Ia-afferents exerted by monosynaptic excitation of the motoneurones. A similar facilitatory action of Ia-afferents excited by muscle stretch (Claus et al. 1988b) and by vibration of the muscle (Claus et al. 1988a) has been described after transcranial stimulation. Conversely, Cowan et al. (1986) have shown that even subthreshold transcranial shocks produce an EPSP in forearm flexor motoneurones which can be detected by H-reflex measurements. The time course of the early facilitatory period differs in magnetic and electric stimu-

Table 3. Mean values and SD of the test H-reflex facilitated by radial superficial nerve (rsn)-stimulation or cortex stimulation in case of electric or magnetic transcranial stimulation. The amplitude of the control H-reflex was normalized to 100%

	Facilitation by cortex stimulation (% of test-HR)	Facilitation by rsn-stimulation (% of test-HR)	Facilitation by cortical and rsn-stimulation (% of test-HR)	Extrafacilitation (% of test-HR)
Electrical cortical stimulation ($n = 7$ subjects)	163 ± 26	185 ± 52	257 ± 78	9 ± 41
Magnetic cortical stimulation ($n = 7$ subjects)	169 ± 28	175 ± 59	347 ± 130	103 ± 67

lation of the brain. The conditioning-test interval is on average 3 ms shorter with magnetic stimulation than it is with electric stimulation. As the median nerve stimulus is the same in both conditions, this finding indicates that magnetic transcranial stimulation stimuli take longer to travel in the cortex or in the central descending tracts and supports earlier observations on the firing characteristics of motoneurones after electric or magnetic stimulation of the brain (Day et al. 1987a). This time lag has been attributed to the different sites of excitation of the two modes of stimulation. Electric stimulation is believed to excite the pyramidal tract neurones directly (Day et al. 1987b; Inghilleri et al. 1989) whereas magnetic stimulation may also act transsynaptically (Day et al. 1987b; Hess et al. 1987).

At a conditioning-test interval of 25–40 ms for electrical and at 22.5–35 ms for magnetic brain stimuli we detected a second period of facilitation. This corresponds to the time period of the LLR and might represent a spatial summation either at the level of the motoneurone, at the motor cortex or at another spinal or supraspinal locus of summation. The existence of a second facilitatory period after median nerve stimulation has already been described in two reports (Deletis et al. 1987; Troni et al. 1988) but could not be demonstrated in a study with stretch evoked reflexes (Claus et al. 1988b). This contradictory results could stem from physiological or technical conditions. Firstly, because the facilitatory effect that results if stretch is applied could depend on cutaneous afferents alone, facilitation could be absent during the time period of the LLR. However, this possibility seems unlikely since the LLR could be demonstrated if the stretched muscle was contracted (Claus et al. 1988b) and the hand muscle LLR are known to be elicited by cutaneous as well as muscle afferents (Deuschl et al. 1985). Secondly, experimental studies are inevitably hampered by safety regulations limiting the number of cortical shocks that can be applied (Agnew and McCreery 1987). Hence, the effects may be too weak to provide statistically significant results. The gain of the LLR depends more on the amount of voluntary contraction (Conrad and Aschoff 1977) than does the H-reflex and all these studies used relaxed conditions.

In the first series of experiments no significant difference could be detected in the facilitation exerted on the LLR by electric or magnetic stimulation. These experiments demonstrated that any attempt to determine more precisely the amount of facilitation on the LLR exerted by electric versus magnetic stimulation requires a more sensitive method. Because a possible spatial summation of two stimuli could be hidden if the output is already saturated by one of stimuli, the conditioning stimuli should remain weak. The strength of transcranial stimulation was therefore kept below the threshold required to produce an MEP in the relaxed muscle. The H-reflex of thenar muscles can only be obtained during contraction but the H-reflex of the forearm flexors can also be elicited in the relaxed muscle (Verrier 1985; Schiepatti 1987). We therefore tested forearm instead of thenar muscles. However, in this condition the stimulus producing the LLR could not be applied at the median nerve as this would have influenced the test H-reflex. Therefore, we used a radial superficial nerve stimulus as a second conditioning stimulus. This cutaneo-muscular reflex is thought to have similar central pathways to the hand muscle LLR (Berardelli et al. 1987) and our experiments showed that the facilitation of the H-reflex following radial superficial nerve stimulation has nearly the same onset and peak latencies as the reflex response obtained by averaging the EMG of the contracting forearm flexors.

The second paradigm of our study therefore compared the facilitation on the conditioned flexor H-reflex exerted by transcranial electric stimulation versus magnetic stimulation. Electrical transcranial stimulation exerted no significant extrafacilitation. However, in four subjects magnetic stimulation produced significantly more facilitation than would be expected by pure addition of the separate effects of radial superficial nerve or transcranial stimulation. In two further subjects, this extrafacilitation just failed significance. In one subject no potentiation was obtained probably because the timing of the different responses was not correct, although this could not be proved as the analysis was performed off-line.

However, our experiments do not exclude a weak extrafacilitation exerted by electric brain stimulation. To test this possibility properly we would need to apply more transcranial stimuli in one session than we consider advisable. Other factors are the amplitude of the control H-reflex and possible non-linear summation if different populationes of motoneurones are exicited by the two different conditioning stimuli (for discussion of these factors see: Fournier et al. 1986; Malmgreen and Pierrot-Deseilligny 1988). However, since these factors are common to electric and magnetic brain stimulation they should not affect the results.

How to explain the prominent extrafacilitation exerted by magnetic brain stimulation? A facilitation at spinal level seems to be unlikely as its amount had been monitored by the facilitation of the H-reflex and was shown to be similar in both conditions. Hence, a supraspinal or even cortical origin of this extrafacilitation seems more likely. Faced with the large amount of possible excitatory or inhibitory effects excerted by cortical stimulation that have been demonstrated experimentally in different species (for review see Creutzfeldt 1983) it remains speculative to comment on the possible intracortical mechanisms mediating the demonstrated extra-facilitation. However, the data would be compatible with a supraspinal pathway of the LLR of hand muscles (Marsden et al. 1973).

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