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# INTERHEMISPHERIC INHIBITION OF THE HUMAN MOTOR CORTEX

BY A. FERBERT*, A. PRIORI†, J. C. ROTHWELL, B. L. DAY, J. G. COLEBATCH‡ AND C. D. MARSDEN

*From the MRC Human Movement and Balance Unit, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG*

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SUMMARY

1. Using two magnetic stimulators, we investigated the effect of a conditioning magnetic stimulus over the motor cortex of one hemisphere on the size of EMG responses evoked in the first dorsal interosseous (FDI) muscle by a magnetic test stimulus given over the opposite hemisphere.

2. A single conditioning shock to one hemisphere produced inhibition of the test response evoked from the opposite hemisphere when the conditioning–test interval was 5–6 ms or longer. We shall refer to this as interhemispheric inhibition. However, the minimum latency of inhibition observed using surface EMG responses may have underestimated the true interhemispheric conduction time. Single motor unit studies suggested values 4–7 ms longer than the minimum interval observed with surface EMG.

3. Interhemispheric inhibition was seen when the test muscle was active or relaxed. Increasing the intensity of the conditioning stimulus increased the duration of inhibition: increasing the intensity of the test stimulus reduced the depth of inhibition.

4. The conditioning coil had to be placed on the appropriate area of scalp for inhibition to occur. The effect of the conditioning stimulus was maximal when it was applied over the hand area of motor cortex, and decreased when the stimulus was moved medial or lateral to that point.

5. The inhibitory effect on the test stimulus probably occurred at the level of the cerebral cortex. In contrast to the inhibition of test responses evoked by magnetic test stimuli, test responses evoked in active FDI by a small anodal electric shock were not significantly inhibited by a contralateral magnetic conditioning stimulus. Similarly, H reflexes in relaxed forearm flexor muscles were unaffected by conditioning stimuli to the ipsilateral hemisphere. However, inhibition was observed if the experiment was repeated with the muscles active.

* Permanent address: Neurologische Klinik der Medizinischen, Fakultaat RWTH Aachen, Pauwelsstrasse o. Nr. D-5100 Aachen, FRG.

† Permanent address: Quinta Clinica Neurologica, Dipartimento di Scienze Neurologiche, Università di Roma 'La Sapienza', Viale dell'Università 30, 00185 Roma, Italia.

‡ Permanent address: Department of Neurology, Prince Henry Hospital, PO Box 233, Matraville 2036, Sydney, Australia.

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6. When the test muscle was relaxed, the amount of interhemispheric inhibition could be increased slightly by voluntary contraction of the muscles in the hand contralateral to the conditioning hemisphere. This effect disappeared if the test muscle was held active throughout the experiment.

7. Magnetic conditioning stimuli over one hemisphere were also capable of affecting on-going voluntary EMG activity in the ipsilateral FDI. Inhibition began 10–15 ms after the minimum corticospinal conduction time to the muscle, and lasted for about 30 ms. The depth of inhibition was approximately proportional to the level of on-going EMG. A similar period of inhibition was also observed in the forearm flexor muscles, but in biceps it was less clear and sometimes preceded by excitation.

8. The interhemispheric inhibition described in these experiments is probably produced via a transcallosal pathway.

## INTRODUCTION

Many studies have shown the importance of the corpus callosum in the transfer of cognitive and sensory information between the hemispheres (e.g. Sperry, 1974). In the field of motor control, such information seems to be involved in controlling visually guided movements (Gazzaniga, 1963, 1969), particularly those of the distal extremity muscles which are thought to be under the predominant control of contralateral corticospinal projections. Control of proximal muscles is less affected by callosal section presumably because of the bilateral connections to proximal muscles via cortico-reticulospinal pathways (Brinkman & Kuypers, 1972). In man, indirect methods of investigating interhemispheric transfer through the corpus callosum have used reaction time studies where stimuli are given to one side of the body, or in one visual hemifield, and movements are made on the contralateral side (e.g. DiStefano, Morelli, Marzi & Berlucchi, 1980; Schieppati, Musazzi, Nardone & Seveso, 1984). Finally, transcallosal transfer of information has been implicated in some pathological conditions. Certain forms of epilepsy have long been suspected to generalize via the corpus callosum (see Reeves, 1985) and Shibasaki, Yamashita & Kuroiwa (1978) and Wilkins, Hallett, Berardelli, Walshe & Alvarez (1984) have reported on the probable transcallosal spread of myoclonic activity in two patients with cortical reflex myoclonus who had bilateral reflex jerks in response to unilateral sensory stimulation. This has been explored in greater detail by Brown, Day, Rothwell, Thompson & Marsden (1991).

The advent of electrical and magnetic methods of transcranial brain stimulation in conscious man has opened the possibility of investigating transcallosal connections in some detail. Cracco, Amassian, Maccabee & Cracco (1989), who repeated in man the original observations made by Curtis (1940) in cat and monkey, recorded an evoked response from one hemisphere after electrical or magnetic stimulation over the motor cortex of the opposite hemisphere. The potential had a minimum onset latency of 8–9 ms, and a duration of 7–15 ms (magnetic stimulation) or 18–44 ms (anodal electric stimulation). They presumed that the potential was due to cortico-cortical transfer between the motor cortices, although it was also possible that sensory areas of cortex could have contributed to the responses they observed. In an attempt to limit testing to motor areas of cortex, a different strategy can be employed. Test stimuli are given over the motor cortex of one hemisphere to elicit

muscle responses on the contralateral side. These test responses are then conditioned by a second stimulus to the opposite hemisphere given at different times beforehand. A brief report using this technique was made by Rossini, Caramia & Zarola (1987) who claimed that scalp electric stimulation over one motor cortex could facilitate responses to stimulation of the opposite side given 8–24 ms later. However, few details of the methodology were given. Indeed, recent reports from both Wasserman, Fuhr, Cohen & Hallett (1990) and from this laboratory (Ferbert, Priori, Rothwell, Colebatch, Day & Marsden, 1990) have suggested the opposite: that stimulation of the motor cortex of one hemisphere can inhibit activity in the contralateral cortex. The purpose of the present paper is to provide a fuller account of our previous experiments. The results reveal a strikingly powerful interaction between the two motor cortices in intact man.

## METHODS

The experiments were performed with the approval of the local ethical committee on fifteen normal healthy volunteers (thirteen men and two women) aged 28–43 years.

Two Novametrix Magstim 200 stimulators (The Magstim Company, Whitland, Dyfed) were used for the experiments. The conditioning stimulator was connected to a figure-of-eight-shaped coil, each loop of the coil having an outer diameter of 7 cm. The peak magnetic field produced by such coils (2·4 T) lies under the region where the two loops meet. We refer to this region as the bar of the figure of eight. The coil was placed with its mid region over the hand area of motor cortex (approximately 6 cm lateral to the vertex). The precise site and orientation of the windings were adjusted to produce the maximal responses in contralateral hand muscles. At different intervals after this stimulus a second magnetic shock was applied to the opposite motor cortex as a test stimulus. This was delivered either by a second figure-of-eight-shaped coil held symmetrically on the contralateral scalp or by a large circular coil (external diameter 14 cm; peak magnetic field 2 T) placed laterally over the hemisphere with its windings passing over the hand area of cortex. In this lateral position the large coil always produced an ipsilateral facial twitch probably due to direct activation of the facial nerve within the skull (e.g. Schriefer, Mills, Murray & Hess, 1988). In two cases, the test shock was given through a small circular coil with an external diameter of 6·5 cm and a peak magnetic field rating of 4·1 T.

In all subjects, surface EMG recordings were made from the first dorsal interosseous (FDI) of each hand with the active electrode placed over the motor point and the reference electrode on the metacarpophalangeal joint. In some subjects we also recorded from biceps and/or flexor carpi radialis with electrodes placed 3 cm apart of the belly of the muscle. Responses were amplified and filtered by Digitimer D150 amplifiers (Digitimer Ltd, Welwyn Garden City, Herts) (time constant 10 ms, low-pass filter to 3 kHz.) Signals were then passed through a CED 1401 laboratory interface (Cambridge Electronic Design, Cambridge) and fed to a personal computer using data collection and averaging programmes (sampling rate of 5–7 kHz per channel) modified to perform conditional averaging. In each set of experiments, test and conditioning shocks at different intervals were randomly intermixed. Ten responses per condition were collected and averaged and their peak-to-peak amplitude was measured. Several blocks of trials were performed in order to construct a complete time course. A block consisted of ten trials each of three to six randomized conditions: the response to a test shock given alone, and the response to the same shock when conditioned by a prior stimulus at different conditioning–test intervals. In this way, with six randomized conditions, three blocks of trials could cover fifteen conditioning–test intervals. Most of the emphasis has been put on intervals of 3–25 ms. The positions of the two stimulators were kept constant throughout each block of trials except in the mapping experiments described below. The peak-to-peak size of conditioned responses was expressed as a percentage of the size of the unconditioned response (= 100%).

In most blocks of trials, responses were recorded either with the subject activating both FDI muscles, or with the subject completely relaxed. In eight subjects the effect of activation and relaxation of the FDI muscle contralateral to the conditioning hemisphere was examined. In this experiment trials were randomized between the active and relaxed state with the experimenter informing the subject before each trial whether to contract or relax the target muscles.

In three subjects we mapped the effective site of the conditioning stimulus using two figure-of-eight coils in the following way. In each block of trials, the coil of the test stimulator was held in a constant position whilst the conditioning coil was moved pseudo-randomly over different scalp locations. The positions tested lay at 2 cm intervals along a medio-lateral line from vertex to ear (five positions in all). Responses to the test and the conditioning stimuli were recorded from both FDI muscles.

In four subjects we compared the effects of a magnetic conditioning shock over one hemisphere on the EMG responses evoked by anodal electrical or magnetic test stimuli given randomly to the opposite hemisphere. The electrical stimuli were provided by a Digitimer D170 (Digitimer Ltd, Welwyn Garden City, Herts) high-voltage electrical stimulator with the cathode fixed at the vertex and the anode 7 cm lateral on a line joining the vertex and the ear. Responses were recorded from the active FDI muscles contralateral to the test hemisphere. The size of the FDI responses to the test stimuli was approximately the same following both types of test shocks and was relatively small to minimize I-wave production by the electrical test shock (cf. Day, Dressler, Maertens de Noordhout, Marsden, Nakashima, Rothwell & Thompson, 1989).

*Single motor unit studies*

In four subjects we conducted experiments on single motor units in the FDI muscle, recorded using concentric needle electrodes (Medelec disposable type DMC25). The details of the technique are given in Day *et al.* 1989. In the present paper, subjects voluntarily discharged the unit at about 10 Hz whilst they received magnetic test stimuli every 4–5 s over the opposite motor cortex. In random trials, this stimulus was preceded by a conditioning stimulus over the opposite hemisphere given 5–10 ms earlier. Three conditions were intermixed: test stimulus alone and test stimulus conditioned at two different intervals; 64–130 trials of each condition were collected and a post-stimulus time histogram (PSTH) of unit discharge constructed. The effect produced by the conditioning shock on the probability of unit firing after the test shock could then be assessed. In these experiments both test and conditioning shocks were delivered by a figure-of-eight coil.

*Effects on voluntary contraction*

In twelve subjects, we investigated the effect of a cortical conditioning shock on on-going voluntary EMG activity. They maintained a small voluntary contraction of the muscle under study (10–15% maximum) whilst magnetic stimuli were given over the hand or arm area of the ipsilateral hemisphere at random intervals every 4–5·5 s. The EMG was rectified and sixty sweeps were averaged.

*Effects on H reflex in forearm flexor muscles*

Test H reflexes were elicited in the forearm flexor muscles of five subjects using bipolar stimulation of the median nerve at the elbow with a Grass S88 stimulator (Grass Instrument Co., Quincy, MA, USA). Stimuli were square-wave pulses of 0·5–1·5 ms duration and at an intensity sufficient to produce H reflexes of approximately 50% maximum size. In each experiment, trials with and without a prior cortical conditioning shock were randomly intermixed. Fifteen sweeps for each condition were acquired. The amplitude of the H reflex in the forearm flexor muscles was measured peak-to-peak, with the size of conditioned responses expressed as a percentage of the size of control responses.

## RESULTS

The principal finding is illustrated in Fig. 1*A*. The subject was sitting relaxed whilst test magnetic stimuli were given over the right hemisphere in order to evoke EMG responses in the left FDI muscle. At different intervals before the test shock, a conditioning magnetic stimulus was given over the left hemisphere. When the test stimulus was given on its own, it evoked a response of about 1·5 mV peak-to-peak amplitude. However, if a conditioning shock of similar intensity (about 20% suprathreshold) was given 6, 7, 12 or 15 ms beforehand, then the response to the test shock was reduced. The time course of this suppression depended on the intensity of the conditioning shock. The graph in Fig. 1*B* illustrates the average time course

evaluated at two different stimulus intensities in six subjects. The onset of inhibition was the same (6–7 ms) with both intensities of conditioning shock, but the duration was longer with the larger shock. Similar results were seen in subjects who exerted a background contraction of the target muscle of about 5% maximum throughout the experiment.

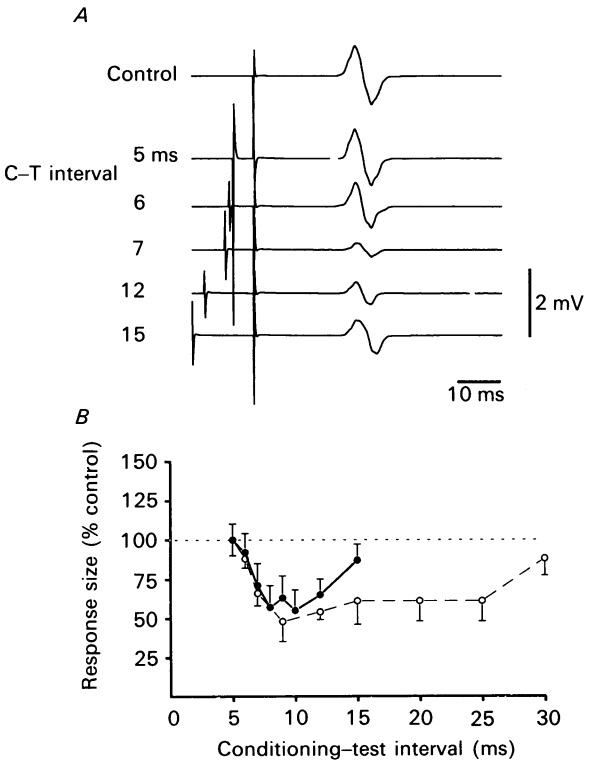


Fig. 1. *A*, effect of a conditioning magnetic stimulus delivered by a figure-of-eight coil (peak magnetic field rating of 2·4 T) over the left motor cortex on EMG responses in the left first dorsal interosseous muscle produced by a magnetic test shock delivered by a second identical coil over the right hemisphere. The top trace shows the response to the test shock given alone. The lower five traces illustrate the effect of a conditioning shock given 5, 6, 7, 12 or 15 ms before the test shock (C–T interval). The traces are aligned to the onset of the test shock. Each trace is the average of ten single trials. The subject was relaxed throughout. The intensity of both the test and the conditioning stimulus was 55% of maximum output. *B*, mean ± 1 S.E.M. time course of interhemispheric inhibition in six different normal subjects using two different intensities of conditioning shock. Responses were recorded in the relaxed FDI muscle, and the size of the conditioned response at each interval has been expressed as a percentage of the size of the test shock given alone (= 100%). The conditioning shock was set to be about 10 (●) or 25 (○)% above the threshold for producing responses in contralateral relaxed hand muscles. As in the subject in *A*, both test and conditioning stimuli were delivered through figure-of-eight coils.

In some blocks of trials in some subjects, we found that the main period of inhibition was preceded by a significant ($P < 0{\cdot}05$, Student's $t$ test on peak-to-peak size of control and conditioned responses) facilitation of the test response at

conditioning–test intervals of between 3 and 5 ms. This facilitation was capricious and would often disappear if the block of trials was repeated, only to reappear again in the same subject on another day. We found it impossible to study in detail. However, we mention it here because it may be related to the short-latency transcallosal facilitation observed in some animal experiments (see Discussion).

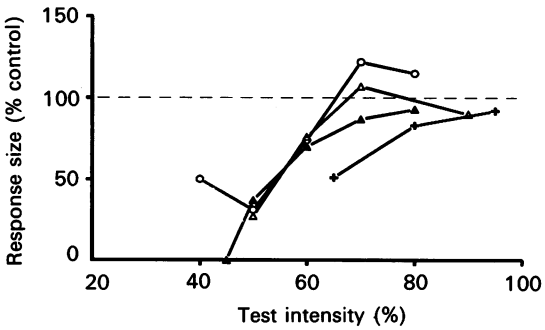


Fig. 2. Effect of the intensity of the test shock to the left hemisphere on the amount of interhemispheric inhibition in the right FDI of four subjects. Each point is the average from ten single trials, using a conditioning–test interval of 10 or 15 ms. The size of the conditioning shock to the right hemisphere was constant. Responses evoked by large test shocks were unaffected by the conditioning stimulus. The conditioning stimulus was delivered through a figure-of-eight coil (maximum output rating of 2·4 T) at an intensity ranging from 50–70% maximum in the different subjects. The test stimulus was given through a large diameter circular coil with a peak output rating of 2 T.

In six subjects, we compared the threshold intensity of the conditioning stimulus needed to produce interhemispheric inhibition (using a conditioning–test interval of 10 ms) with the threshold for eliciting a motor response in pre-activated muscles of the hand contralateral to the conditioning stimulus. In three of the subjects the inhibitory threshold was approximately the same as the motor threshold. In the remaining three, the inhibitory threshold was an average of 20% higher than motor threshold.

The amount of inhibition also depended on the size of the test shock; the larger the test shock, the less inhibition was evoked by a given size of conditioning stimulus. Results from four subjects are shown in Fig. 2. In all the results which follow, the test stimulus evoked an EMG response of 0·5–3 mV peak-to-peak, using average stimulus intensities of 40–60% of the output of the stimulator.

*Mapping the effective area for interhemispheric inhibition*

In three subjects we used a figure-of-eight coil with its stimulating area aligned in the antero-posterior direction to map the medio-lateral extent of the inter-hemispheric inhibitory effect on the first dorsal interosseous muscle. Conditioning stimuli were given to the right hemisphere, and test stimuli to the left hemisphere. During this experiment the subjects contracted both FDI muscles to the same extent, so that we could measure: (*a*) the size of EMG responses evoked directly by the conditioning shock in the left FDI when the stimulus was given at different sites, and (*b*) the amount by which the same conditioning stimulus could inhibit

test responses evoked in the right FDI (Fig. 3). The best point for evoking interhemispheric inhibition, 4–8 cm lateral to the vertex, coincided with the best point for evoking EMG responses in the contralateral FDI muscle. Movement of the conditioning coil more medial, nearer the vertex, or more lateral, nearer the ear, reduced the amount of interhemispheric inhibition.

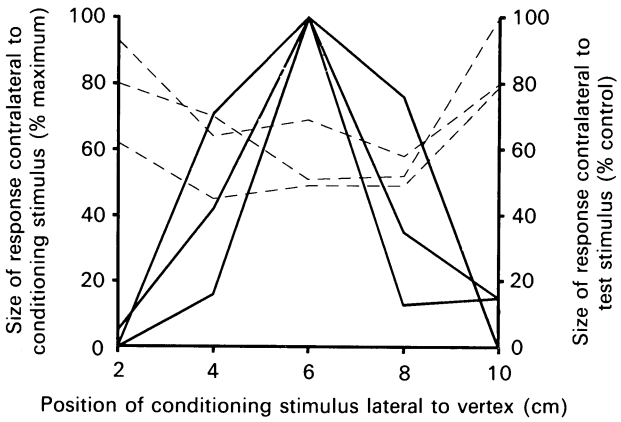


Fig. 3. Effect of changing the location of the conditioning stimulus. The graphs show how the amount of both interhemispheric inhibition and the size of the EMG response to the conditioning stimulus alone were affected by moving the conditioning coil. Results are shown in three subjects using a conditioning–test interval of 15 ms. The dashed line plots the percentage interhemispheric inhibition produced by the conditioning shock delivered to the right hemisphere on the size of the response in the right FDI evoked by the test shock to the left hemisphere. The continuous lines plot the size of the response evoked in the left FDI by the conditioning stimulus given alone to the right hemisphere. Sizes of the contralateral responses have been normalized for each subject to the maximum seen in each individual. Results at each point are calculated from the average of ten trials in each subject. In each block of trials the position of the conditioning coil was varied randomly in 2 cm steps along a line from the vertex to the ear. The figure-of-eight coil was held with the bar of the eight oriented in the anterior–posterior direction.

*Effect of activating the FDI muscle contralateral to the conditioning stimulus*

In eight subjects we tested whether interhemispheric inhibition varied during voluntary contraction of the FDI contralateral to the conditioning cortical stimulus. Such a contraction increases the size of EMG responses produced in contralateral muscles by the conditioning stimulus, but we were intrigued whether it would affect the amount of interhemispheric inhibition as compared with that seen in the relaxed state.

Two sets of experiments were conducted: the results are summarized in Table 1. In all experiments, the test muscle was the right FDI. Responses elicited in this muscle by stimulation of the left hemisphere were inhibited by a conditioning shock given over the right hemisphere 10 ms earlier. The intensities of the two shocks were such as to produce equal-sized EMG responses in the respective contralateral muscles. In the first set of experiments, subjects held the right FDI relaxed throughout, and on random trials, as instructed by the experimenter, contracted the left FDI by 5–10% maximum. Contracting the left FDI had two effects. The most

TABLE 1. Effect of activation of the left FDI on the amount of interhemispheric inhibition recorded in the right FDI

| | Right relaxed | | | Right active | | |
|---|---|---|---|---|---|---|
| | Size of conditioned response (% control) | | Size of right side responses | Size of conditioned response (% control) | | Size of right side responses |
| Subject | Left relaxed | Left active | (% control) | Left relaxed | Left active | (% control) |
| 1 | 39 | 28 | 112 | 34 | 28·5 | 109 |
| 2 | 38 | 33·5 | 118 | 47·5 | 61·5 | 103 |
| 3 | 22 | 25 | 161 | 34 | 34 | 100 |
| 4 | 31 | 21 | 171 | 66 | 65 | 96 |
| 5 | 43 | 31·5 | 164 | 87 | 93 | 101 |
| 6 | 55·5 | 47 | 103 | 65·5 | 67 | 100 |
| 7 | 80·5 | 43 | 203 | 81 | 80 | 100 |
| 8 | 39 | 31 | 168 | 75 | 80 | 100 |
| Mean | 43·5 | 36·2** | 150 | 61·2 | 59·9 | 101 |
| S.E.M. | 6·3 | 5·9 | 12·4 | 7·3 | 8·9 | 1·3 |

Test responses were evoked in the right FDI muscles by magnetic stimuli to the left hemisphere and were conditioned by magnetic stimuli over the right hemisphere, using a conditioning–test interval of 10 ms. The two halves of the table show results obtained when the right FDI was held relaxed or active throughout the experiment. The first two columns in each half show the amount of interhemispheric inhibition (expressed as (size of conditioned response)/(size of control response)%) when the left side was relaxed or active. The third column shows how contraction of the left side affected the size of control responses evoked in the right FDI. The same cortical stimulus intensities were used when the right FDI was relaxed and when it was active. Because of this the absolute size of control responses in right FDI (with the left side relaxed) was different depending on the state of contraction of the muscle. Control responses in the relaxed right FDI averaged $0{\cdot}8 \pm 0{\cdot}4$ mV peak to peak, but increased to $3{\cdot}0 \pm 0{\cdot}3$ mV peak to peak when the right side was active. Values are the average of twenty trials in each subject. ** Student's paired $t$ test between values in column 1 and 2: $P < 0{\cdot}005$.

obvious was that the size of control responses evoked in the relaxed, right, FDI was increased to 150 ± 12·4 % (mean ± S.E.M.) of control values. This effect has been noted previously by Hess, Mills & Murray (1986). However, despite this increase in size of control responses, which might have been expected to be accompanied by a decrease in the percentage interhemispheric inhibition (Crone, Hultborn, Mazieres, Morin, Nielsen & Pierrot-Deseilligny, 1990) contraction of the left FDI was also accompanied by a slight, but significant increase in the amount of interhemispheric inhibition produced by a conditioning shock to the right hemisphere. Responses in the right FDI were reduced to 43·5 ± 6·3 % of their control size when the left side was relaxed, but were reduced to 36·2 ± 5·9 % of their control size when the left side was active (paired $t$ test $t = 4·4$, $P < 0·005$).

The second set of experiments was the same as the first, except that subjects kept the right FDI active throughout whilst they randomly activated or relaxed the left muscle. In these experiments, contraction of the left FDI had no effect on the size of control responses in the right FDI. Similarly, contraction of the left side had no influence on the amount of interhemispheric inhibition detected in the active right FDI.

*Inhibitory effects in biceps*

Most experiments were performed using the FDI muscle. However, in six subjects, we also examined whether interhemispheric inhibition could be demonstrated in the biceps muscle using a conditioning–test interval of 10 ms. Because of the high threshold for obtaining responses in relaxed biceps, the experiments were performed during tonic voluntary contraction of the muscle. The other arm was held relaxed throughout. Inhibition could be demonstrated in all subjects. The average size of conditioned responses was 77 ± 3·3 % (mean ± S.E.M.); (range 64–88 %) of control values.

*Electrical versus magnetic test stimuli*

In order to analyse the level of the neuraxis at which interhemispheric inhibition took place we compared in four subjects the effect of a magnetic conditioning stimulus to one hemisphere on the size of responses evoked by either a magnetic or an electrical test shock to the opposite hemisphere. Electrical and magnetic stimuli are thought to activate the same descending pathways, but in different ways (see Day *et al.* 1989; Edgley, Eyre, Lemon & Miller, 1990). Magnetic stimuli may excite the initial segment of pyramidal tract neurones, or the synaptic input onto these neurones. In contrast, electrical stimuli probably activate the pyramidal axons directly within the white matter. Thus, if interhemispheric inhibition is affecting cortical excitability, test responses to electrical stimulation would be unaffected whilst those to magnetic stimulation would be reduced (see Discussion). The two types of test stimuli were intermixed randomly and conditioning–test intervals of 3–15 ms were explored. The test muscles were active throughout the experiment and the intensity of the stimulus was adjusted so that the responses to electrical or magnetic shocks were of approximately the same size. In addition, a relatively low intensity of electrical stimulation was used in order to minimize indirect (trans-synaptic) activation of cortico-spinal neurones (see Day *et al.* 1989). Figure 4*A*

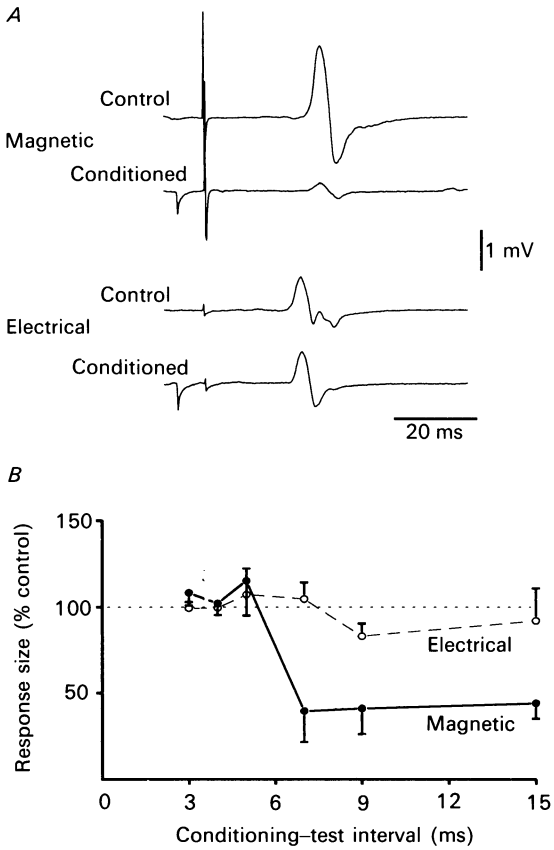


Fig. 4. *A*, example in a single subject of the effect of a magnetic conditioning stimulus over one hemisphere on the size of EMG responses evoked by magnetic (upper two traces) or electrical (lower two traces) stimulation of the opposite hemisphere. Each pair of traces shows the average (of ten trials) response to the test shock given alone (control) or with the response conditioned by a preceding magnetic shock (conditioned). The conditioning–test interval was 9 ms in both pairs of traces. The response to magnetic test stimuli is inhibited, whereas the response to electrical test stimuli is almost unchanged, apart from loss of a second positive component which had been present in the control. The four experimental conditions were applied pseudo-randomly in one block of trials. *B*, comparison of the time course of interhemispheric inhibition from responses elicited by electrical or magnetic test stimuli in four subjects. Points are means ± S.E.M. (Paired *t* tests comparing mean inhibition of electrically and magnetically evoked test responses showed significant ($P < 0{\cdot}05$) differences at intervals of 7, 9 and 15 ms.) Magnetic conditioning stimuli were given via a figure-of-eight coil having a maximum output rating of 2·4 T. Stimulation intensity ranged from 50–67 %. Magnetic test stimuli were given through a large round coil having a maximum output rating of 2 T. Stimulation intensities ranged from 45–74 %. The mean peak-to-peak size of the control EMG response evoked by magnetic stimuli (2·7 mV) was slightly larger than control responses evoked by electrical test stimuli (2·2 mV).

illustrates a typical example of the results from one subject with a conditioning–test interval of 9 ms. Both the negative and positive phases of the EMG response to the magnetic test stimulation were strongly inhibited by a prior conditioning magnetic

shock. However, the only effect of the conditioning magnetic shock on the response to test electrical stimulation was inhibition of the later positive inflections in the surface EMG potential. The peak-to-peak size was virtually unchanged. Following the analysis of Day *et al.* (1989), it seems likely that the later inflections in the surface EMG response to electrical stimulation are caused by arrival of I-wave volleys at the spinal cord. If so, then in this particular example these I-waves may have been inhibited by the conditioning shock whereas the initial D-wave was unaffected.

The time course of interhemispheric inhibition in all four subjects is shown in Fig. 4*B*. The responses to magnetic test stimuli were clearly inhibited at intervals of 7, 9 and 15 ms, whereas those to electrical test stimuli were virtually unchanged. Note that the average size of control responses evoked by magnetic test stimuli (2·7 mV) was slightly larger than those evoked by electrical test stimuli (2·2 mV). According to the data in Fig. 2, this should have made the electrical responses, if anything, more susceptible to inhibition than the magnetic responses.

*Single motor unit studies*

We were concerned that, using magnetic test shocks, the onset of inhibition (6–7 ms) may have underestimated the minimal interhemispheric conduction time. The main reason for this is that a test magnetic stimulus is known to produce more than one descending volley in the pyramidal tract. These volleys last for a period of 5 ms or more after the stimulus (e.g. Kernell & Wu, 1967) and all of them, whether in active or relaxed muscle, may contribute to the peak-to-peak size of the surface EMG potential. If the conditioning shock were given at a short conditioning–test interval, the inhibitory volley might not arrive early enough at the test hemisphere to influence the first descending volley. Nevertheless, it might be able to interact with the second, or later, descending volleys set up by the test stimulus. If one or more of these volleys were decreased in size, then the total descending excitation evoked by the test stimulus would be reduced, and the peak-to-peak size of the EMG response evoked by the test stimulus would be smaller than expected. Thus, although the interval between conditioning and test stimuli was short, this interval would not correspond to the time taken for the inhibitory conditioning volley to reach the test hemisphere. Inhibition might actually reach the test hemisphere several milliseconds after the test shock was given. A similar argument has been used by Katz, Pericaud & Rossi (1991) in experiments comparing the latency of reciprocal inhibitory effects on H reflexes and tendon jerks evoked in the biceps muscle.

This reasoning was confirmed by observations of single motor unit behaviour. In six motor units from the FDI of four different subjects, we constructed a PSTH of firing probability to the test stimulus given alone. We then compared this with the PSTH evoked when the shock was preceded by a conditioning shock to the opposite hemisphere. An example of the behaviour of one of these units is illustrated in Fig. 5. The test shock evoked two main peaks of increased firing lasting for a period of 4 ms or so. These peaks are thought to reflect the multiple descending volleys in the pyramidal tract set up by the magnetic shock (Day *et al.* 1989). If a conditioning stimulus was given 6 ms beforehand, the second peak and the small number of counts which followed it were reduced in size, but not the first peak. When the interval was increased to 10 ms, all peaks were affected. For this particular unit (unit JI in Table

2), unequal numbers of stimuli were used to construct the PSTHs in each condition. If this is taken into account, then the proportional change in the size of the peaks following the conditioning shock is greater than the difference in the absolute number of counts.

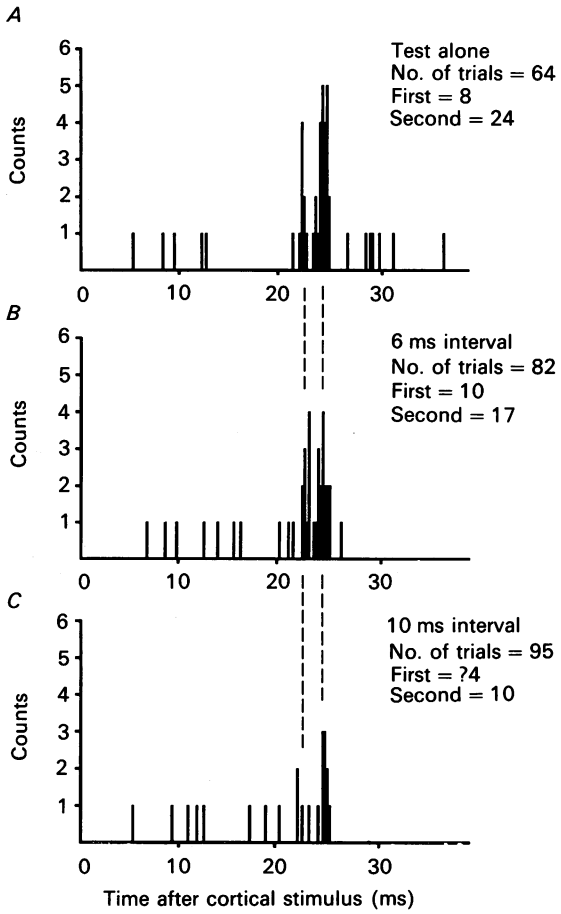


Fig. 5. PSTHs of the firing pattern of a single motor unit in FDI after magnetic test stimuli given over the contralateral motor cortex at $t = 0$ ms. The three traces show the PSTH to the test shock given alone (*A*), and when preceded (on random trials) by a conditioning stimulus to the opposite cortex given 6 (*B*) or 10 ms (*C*) earlier. The number of counts in the two main peaks of the PSTH (joined by the vertical dashed lines) together with the total number of stimuli used to construct each histogram is noted to the right of each trace. With a conditioning–test interval of 6 ms, only the second peak (and the small number of counts which follow it) is reduced in size. At 10 ms, both peaks are affected. Note that at this conditioning–test interval, there is no clear initial peak. However, four counts do occur within the time period of the first peak as defined in trials with the test shock alone. This value was used, as a conservative estimate, for statistical comparisons (see Table 2 and main text).

Details of the data from all six units are given in Table 2. When the test stimulus was given alone, it usually generated two or three peaks of increased firing in the PSTH. If there were only two clear peaks, then the counts in each were analysed

TABLE 2. Suppression of single motor unit discharge evoked from a contralateral test shock by an ipsilateral conditioning stimulus given 5–7 ms or 10 ms earlier

| Unit (no. of trials) | Conditioning–test interval = 6–7 ms | | | | Conditioning–test interval = 10 ms | | | |
|---|---|---|---|---|---|---|---|---|
| | First half of PSTH peak | | Second half of PSTH peak | | First half of PSTH peak | | Second half of PSTH peak | |
| | Control | Conditioned | Control | Conditioned | Control | Conditioned | Control | Conditioned |
| JI (64*) | 8 | 10 | 24 | 17 | 8 | 4 | 24 | 10 |
| JII (75) | 26 | 29 | 13 | 1 | — | — | — | — |
| P (130) | 19 | 16 | 61 | 38 | 19 | 12 | 61 | 26 |
| B (80) | 12 | 12 | 36 | 19 | 12 | 11 | 36 | 17 |
| TI (75) | 11 | 21 | 32 | 13 | 11 | 8 | 32 | 5 |
| TII (86) | 6 | 6 | 59 | 53 | 6 | 4 | 59 | 8 |

Recordings were made from motor units in the right FDI muscle after magnetic test stimuli over the left motor cortex. The stimulus always evoked two or three sub-peaks of increased firing probability lasting for a total of 4–6 ms. If there were only two clear peaks, then each was analysed separately. If there were three peaks, or the division between peaks was unclear, we divided the total duration of increased firing into two halves, each 2–3 ms in duration, and analysed the effect of a prior ipsilateral conditioning shock on the counts in each half. All six units were studied with a conditioning–test interval of 6–7 ms; five of the units were also studied with an interval of 10 ms. The number in brackets next to the unit identifier gives the number of stimuli given in each block of trials. * In this unit, there were unequal numbers of stimuli given in each condition. Control trials had sixty-four stimuli, 6–7 ms interval had eighty-two stimuli, and 10 ms interval had ninety-five stimuli.

separately. If there were three peaks, or the division between the peaks was unclear, the total duration of increased firing was divided into two and the counts in each half analysed separately. In all cases, when the ipsilateral conditioning shock was given only 6–7 ms before the test shock, there was a decrease in the size of the second

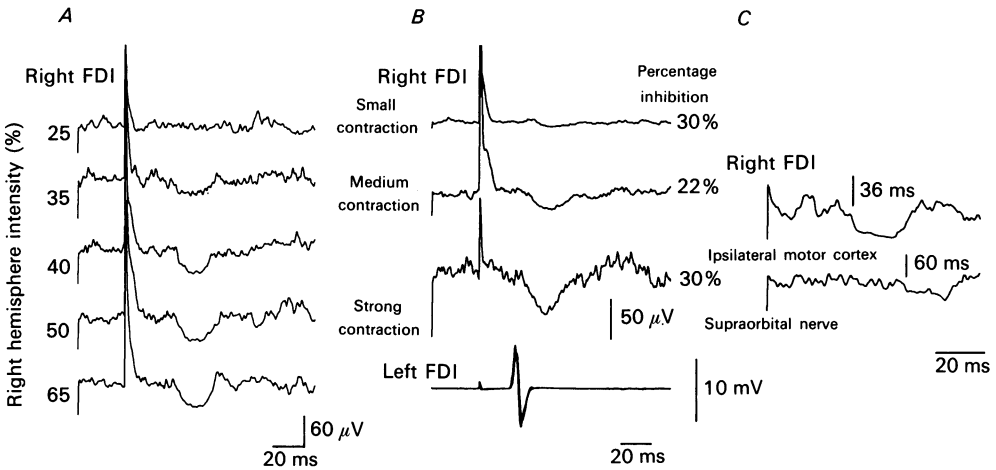


Fig. 6. *A* and *B*, examples from one individual of the effect of a magnetic conditioning stimulus given over the right hemisphere on the level of on-going voluntary EMG activity in the right FDI muscle. The conditioning stimulus produces a stimulus artifact which is followed about 30–35 ms later by a period of inhibition in the EMG trace. The traces in *A* illustrate the effect of changing the intensity of the conditioning shock (values given to the left of each trace). The amount of inhibition increased at higher conditioning strengths, but the time course remained approximately constant. In *B*, the results of three experiments are shown in which the subject performed either a small, medium or strong contraction of the target muscle. Each trace is the average of forty trials. The time course of inhibition was approximately the same at all three levels of contraction. Similarly the amount of inhibition (expressed as the decrease in area of the traces over the inhibitory period compared with control levels of activity), was also approximately the same in each trace (see percentage figures to the right of each record). The bottom superimposed traces show that the average size of EMG responses in the relaxed left FDI muscle produced by the conditioning shock was the same in all three blocks of trials. *C*, comparison of the effect of a magnetic conditioning shock to one hemisphere with electrical stimulation of the supraorbital nerve on the same side of the head on the level of voluntary EMG activity in the ipsilateral FDI muscle. As in the traces in *A* and *B*, the magnetic conditioning shock evokes a short-lasting period of inhibition starting about 36 ms after the stimulus. In contrast, the supraorbital nerve shock produces a smaller period of inhibition with an onset latency of about 60 ms.

peak/half of the PSTH increase, but no change in the number of counts in the first peak/half. (Chi-squared test on the combined data from each unit: first peak/half $\chi^2 = 0{\cdot}4$, degrees of freedom (d.f.) $= 1$, $P > 0{\cdot}05$; second peak/half $\chi^2 = 33{\cdot}7$, d.f. $= 1$, $P < 0{\cdot}001$.) When the conditioning–test interval was increased to 10 ms, there was a decrease in size of both peaks/halves of the PSTH increase. (Chi-squared test on combined data: first peak/half $\chi^2 = 4{\cdot}4$, d.f. $= 1$, $P < 0{\cdot}05$; second peak/half $\chi^2 = 125$, d.f. $= 1$, $P < 0{\cdot}001$).

*Effects of conditioning magnetic stimuli on ipsilateral voluntary EMG activity*

In the experiments above, the test response was produced by an externally applied stimulus. The question is whether a conditioning shock can also modulate ipsilateral on-going voluntary EMG activity in a way predictable from its effect on transcranial

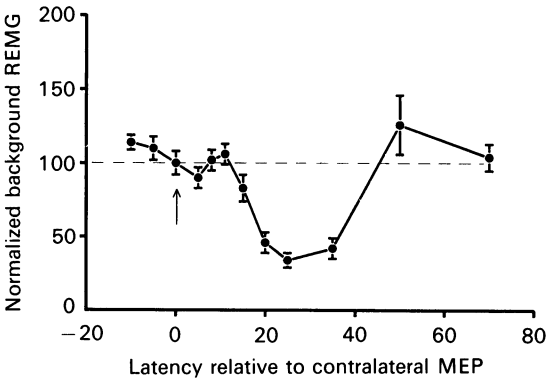


Fig. 7. Combined results from twelve of the subjects (mean ± S.E.M.) showing the effect of a magnetic conditioning shock over one hemisphere on the level of voluntary rectified EMG activity (REMG) in the ipsilateral FDI muscle. In this graph, latencies of the response were aligned to the onset of the EMG response that occurred in the FDI contralateral to the stimulus (MEP: arrow). This procedure compensates for differences in height and arm length of the subject. It means that the stimulus was given some 20–22 ms before time zero. About 12–15 ms (13·4 ± 3·2 ms; mean ± S.D.) after the onset of the direct response in the contralateral FDI, on-going EMG activity in the ipsilateral FDI is reduced for a period of about 30 ms.

test stimuli. In twelve subjects, we gave a conditioning magnetic stimulus to one hemisphere whilst the subject tried to maintain a constant level of voluntary EMG activity in the ipsilateral FDI muscle. In all cases, the stimulus modified the rectified, averaged surface EMG. Figure 6 illustrates examples of the effect in one individual. About 30–35 ms after the conditioning shock, there was suppression of the on-going voluntary activity. This lasted for some 35 ms, before EMG activity returned to baseline values. Increasing the intensity of the conditioning shock increased the depth of suppression but had little effect on the time course (Fig. 6*A*). The level of background EMG activity was not an important factor in demonstrating this suppression: the depth of suppression was approximately proportional to the level of background EMG activity in the muscle (see Fig. 6*B*).

Figure 7 shows the average time course of suppression in all subjects. In order to combine data from different individuals, the on-going EMG before the stimulus has been normalized to a value of 100 %, and changes at each time interval expressed as a percentage of that value. In addition, the time courses have been realigned according to the conduction time from brain to muscle (evaluated using supra-threshold magnetic stimuli to the contralateral cortex). This time is expressed as time zero, meaning that the cortical conditioning shock was given from 20 to 22 ms beforehand, depending on the height of the subject and the length of his/her arm. Inhibition began 12–15 ms (13·4 ± 3·2 ms (mean ± S.D.)) after the minimum con-

duction time from brain to muscle. The depth of inhibition of the on-going EMG was quite large (to 25% of control levels) as compared with the average inhibition using the double shock technique (about 50%; see Fig. 1).

We also examined the suppression in forearm flexor and biceps muscles of nine subjects. In all of them, we observed clear suppression of EMG activity in the flexor carpi radialis muscle, but in biceps, the results were variable. Only three subjects showed a pattern of suppression followed by a return to baseline similar to that seen in the FDI muscle. In three other subjects there was a short latency ($9{\cdot}5 \pm 5{\cdot}1$ ms; S.D., after contralateral response) facilitation followed by a longer-lasting suppression, and in the remaining subjects no clear effect could be observed.

*Effect of supra-orbital nerve stimulation on voluntary EMG activity in the FDI muscle*

It is well known that stimulation of afferents in the trigeminal nerve can evoke a silent period in many muscles of the face and neck. The question arises as to whether the period of suppression of EMG activity in hand muscles produced by magnetic conditioning stimuli applied to the ipsilateral scalp could be caused by a similar reflex event. To test whether stimulation of trigeminal afferents could influence EMG activity in FDI we applied electrical or magnetic stimuli (at four times perceptual threshold) to the supra-orbital nerve in four subjects. This produced a slight (to 70% baseline levels) depression in the on-going EMG activity of the ipsilateral FDI muscle. However, the latency of the effect, at 45–60 ms, was 15–30 ms longer than the inhibitory latency following transcranial stimulation (see Fig. 6*C*). There was another reason for supposing that stimulation of trigeminal afferents was not necessary to produce suppression of voluntary EMG activity. In two subjects we found that with the conditioning coil in its usual position, the threshold for a blink reflex (as judged from EMG records from orbicularis oculi) was 35 or 45% of the stimulator output, whereas the threshold for cortical suppression was 25% in both of them. If we regard the blink reflex as a sensitive indicator of activity in trigeminal reflex pathways, then this suggests that the latter is unnecessary for producing the short latency suppression of ipsilateral activity in hand muscles.

*Effect of magnetic conditioning stimuli on H reflexes evoked in ipsilateral forearm muscles.*

The experiments described above rely on detecting inhibition in pre-activated muscles. In a final series of experiments we tested whether inhibition also could be observed in the relaxed state. In five subjects we evoked H reflexes in the relaxed forearm flexor muscles at 20, 30 and 40 ms after a conditioning magnetic stimulus over the ipsilateral hemisphere. Given an average latency of 18 ms, the H reflex occurred between 38 and 58 ms after the conditioning shock. In active muscle, the experiments described above show that such a conditioning stimulus would normally produce a silent period in the EMG from about 30–60 ms. Despite this, in the relaxed state, there was no change in the size of the H reflex at any of the three intervals. (Size of conditioned H reflex as a percentage of control: $105 \pm 12$, $104 \pm 11$, $115 \pm 18$ (mean $\pm$ S.E.M.) at conditioning–test intervals of 20, 30 and 40 ms respectively.) A different result was obtained when the experiment was repeated whilst subjects

voluntarily pre-activated the muscle. The H reflex was significantly ($P < 0.05$) inhibited at a conditioning–test interval of 30 ms. (Size of conditioned H reflex as a percentage of control at 20, 30 and 40 ms was $82 \pm 19$, $68 \pm 17$, $108 \pm 11$ respectively.)

## DISCUSSION

### *Results obtained with double magnetic stimulation*

The present experiments have shown that a magnetic stimulus over one hemisphere can inhibit EMG responses evoked by magnetic stimulation of the opposite hemisphere given 6–30 ms later. This effect appeared to be due to stimulation by the conditioning shock of some localized structure within the brain. The inhibitory effect on responses in the FDI muscle was maximum when the conditioning coil was placed 6 cm lateral to the vertex, approximately over the hand area of motor cortex, and became smaller if the coil was moved away from this position. The inhibition was not caused by spread of the conditioning stimulus to the opposite hemisphere. When the conditioning coil was moved medially, nearer to the vertex, the amount of inhibition was reduced.

Two lines of reasoning suggest that the inhibition was exerted at a cortical level. (i) In relaxed subjects, stimulation over one hemisphere had no effect on the size of the H reflexes in ipsilateral forearm flexor muscles. This implies that inhibition of a cortically evoked test response was not caused by activity in a direct ipsilateral inhibitory pathway to spinal motoneurones. (ii) In double cortical shock experiments, the conditioning stimulus had little effect on responses produced by electric stimulation in contrast to the clear inhibition of responses evoked by magnetic stimulation. With the same stimulating techniques as those used in the present experiments it has been shown that magnetic stimuli may activate corticospinal neurones either trans-synaptically (Day, Thompson, Dick, Nakashima & Marsden, 1987; Day *et al.* 1989) or at the initial segment (Edgley *et al.* 1990), whereas electrical stimuli activate the axons of the same cells in the white matter. The result is that the size of responses produced by magnetic brain stimulation is influenced much more by the level of cortical excitability than those evoked by transcranial electric stimulation (Datta, Harrison & Stephens, 1989; Day, Reischer, Struppler, Rothwell & Marsden, 1991; Ugawa, Day, Rothwell, Thompson, Merton & Marsden, 1991). Lack of inhibitory effects on electrically evoked responses in the present experiments suggests that inhibition of responses to magnetic test shocks was occurring at a cortical level.

What is the mechanism of this inter-hemispheric inhibition? The short latency of the effect suggests that a relatively direct pathway is involved. However, in double shock experiments, the precise timing was difficult to estimate for two reasons: (i) if Day *et al.* (1989) are correct in assuming that magnetic stimulation activates pyramidal neurones trans-synaptically, then it may take 1–2 ms for a single test stimulus to excite corticospinal neurones; (ii) a single test shock can produce repetitive activity in pyramidal neurones lasting 3–5 ms or so. Thus, taking the worst-case figures, the last corticospinal volley produced by a test magnetic stimulus may leave the cortex up to 7 ms after the test shock was given. Arrival of interhemispheric inhibition at this time would reduce the size of the last descending

motor volley, and, since all volleys may contribute to the peak-to-peak size of the EMG response, this would result in inhibition of the magnetically evoked test response. Such late arrival of interhemispheric inhibition could be observed in single motor unit experiments, where short conditioning–test intervals produced inhibition only in the later excitatory volleys reaching spinal motoneurones, whereas longer intervals resulted in a reduction in the size of all volleys. The net result is that although the minimum conditioning–test interval for interhemispheric inhibition was about 6 ms using the double shock technique, the true time taken for the conditioning volley to reach the test hemisphere may have been anything up to 13 ms.

An interhemispheric conduction time of 13 ms is quite short and although it is possible that the effects we observed were due to conduction from one cortex to the other through subcortical structures, we favour the hypothesis that the major part of the effect was due to conduction in a transcallosal pathway. This is supported by preliminary observations on a patient with agenesis of the corpus callosum (Rothwell, Colebatch, Britton, Priori, Thompson, Day & Marsden, 1991) in whom such inhibition was absent. The timing is also consistent with measurements made by Cracco *et al.* (1989), using evoked potential recordings over one hemisphere after magnetic or electric stimulation of the opposite hemisphere. Similar values were obtained by Shibasaki *et al.* (1978), Wilkins *et al.* (1989) and Brown *et al.* (1991) in their studies of patients with generalized cortical myoclonus. Methods of estimating transcallosal conduction time in man by using reaction-time techniques have yielded a wider range of values from 2 to 20 ms (DiStefano *et al.* 1980; Schieppati *et al.* 1984; Saron & Davidson, 1989).

In animal experiments, it has been shown that neurones which give rise to the fibres of the corpus callosum represent a neuronal population separate from those which project to the corticospinal tract (Catsman-Berrevoets, Lemon, Vanburgh, Bentivoglio & Kuypers, 1980). This would account for the present finding that in three subjects, there was a clear difference in the stimulation threshold for interhemispheric inhibition and contralateral motor responses. We do not know whether the effects observed were due to antidromic or orthodromic activation of callosal fibres. In the cat, effects of callosal stimulation probably depend on both antidromic and orthodromic activity (Spidalieri, Guandalini & Franchi, 1986). Inhibitory effects probably depend on activation of local inhibitory interneurones (e.g. Berlucchi, 1990).

*Effects on ipsilateral tonic EMG activity*

Stimulation over one hemisphere produced a short period of suppression of tonic voluntary EMG activity of the ipsilateral FDI and flexor carpi radialis muscles. The initial part of this effect was not due to a non-specific inhibition from afferents in the trigeminal nerve since supra-orbital stimulation failed to evoke inhibition at the same latency. Trigeminal inhibition of voluntary EMG activity in FDI only occurred at longer latency and at higher stimulus intensities, and was relatively small compared with the effect of transcranial magnetic stimulation.

It seems most likely that suppression of on-going voluntary EMG was the result of a reduction in the effectiveness of voluntary activation of the motor cortex by interhemispheric inhibitory mechanisms. The latency of suppression, at 12–15 ms

later than the minimal corticospinal conduction time, compares well with the latency of transcallosal effects estimated above. However, it is difficult to make exact comparisons between the onset latencies using the two techniques. First, it is difficult to estimate the precise onset of inhibition in records of tonically active EMG. Second, there is no guarantee that the same population of pyramidal tract neurones is activated during a small voluntary contraction as is activated by a magnetic test stimulus. If the populations differ, then their axon conduction velocities may also be different and the onset latency of inhibition would be affected.

There were two points of difference between inhibition detected by double cortical stimulation and suppression of voluntary EMG activity. (i) The depth of inhibition was greater in the tonic voluntary EMG than in the double shock experiment. This may be because relatively few pyramidal neurones discharge in the voluntary task, and hence are more readily inhibited than the large synchronous volleys set up by a magnetic test stimulus. (ii) The duration of voluntary suppression appeared approximately constant, even with different intensities of conditioning shock. In the experiments with two cortical stimuli, the duration of inhibition increased as the conditioning intensity was increased. Possibly this can be explained by activation during voluntary effort of other descending cortical pathways in addition to the large diameter component of the corticospinal tract.

Unlike the situation in FDI and forearm flexors, the behaviour of ipsilateral voluntary EMG activity in biceps was very variable from subject to subject, despite the fact that a conditioning stimulus had always inhibited magnetically evoked test responses in the same muscle. We can only speculate on the reasons for this discrepancy. One possibility is that the fast-conducting corticospinal system is less active during voluntary contraction of biceps than during voluntary contraction of FDI. Thus cortical inhibition has a smaller effect on the size of the voluntary descending outflow to biceps than the FDI. Magnetic stimulation of motor cortex, in contrast, activates all muscles via the largest corticospinal fibres, so that the inhibitory effect is seen in both biceps and FDI. If this explanation is correct, then evaluation of transcallosal inhibition may prove to be a useful method of documenting the relative role of large corticospinal fibres and other structures in producing muscle activation during different types of movement.

*Transcallosal inhibition*

Consideration of data from animal experiments reveals two apparent problems with our suggestion that the interhemispheric inhibition observed here was produced by a transcallosal mechanism. First, there are fewer callosal connections between hand areas of motor cortex, where we observe maximum inhibitory effects, than between regions controlling the arm and trunk (Jenny, 1979; Pappas & Strick, 1981; Gould, Cusick, Pons & Kaas, 1986). However, even if they are sparse, the connections do seem to be effective. Stimulation of the corpus callosum in the monkey has the same effect on precentral neurones related to distal muscle groups as it has on neurones involved in proximal muscle contractions (Matsunami & Hamada, 1984).

The second difference between the present results in man and transcallosal data collected in animals is that in general, stimulation to one motor cortex, or to the callosal fibres themselves, seems to evoke an early contralateral period of facilitation, followed by a longer-lasting inhibition (Purpura & Girado, 1950; Asanuma &

Okamoto, 1959; Asanuma & Okuda, 1962; Matsunami & Hamada, 1984). In the present study we failed to find any convincing evidence for a period of transcallosal facilitation.

One possible reason for this is that, according to Asanuma & Okuda (1962), stimuli applied to a small area of cortex produce excitatory effects in strictly homotopic areas of contralateral cortex, and inhibition in a wide area of surrounding cortex. In the present experiments our conditioning stimulus inevitably excited a considerable area of cortex. It might be that under these conditions the point-to-point facilitation described by Asanuma & Okuda (1962) is overwhelmed by the accompanying surround inhibition. Another possible reason for the lack of transcallosal facilitation is that a magnetic test shock produces a prolonged volley of descending impulses in corticospinal pathways. If transcallosal excitation is followed by inhibition, then excitation of the early part of the descending volley might be masked by inhibition of the later part, particularly if there were any dispersion in the transcallosal volley. Only if excitation were critically timed to affect the late part of the volley would any facilitation of the final EMG response be seen. Interestingly, this condition may have occurred in one experiment of the present series. In unit TI of Table 2, a conditioning stimulus at 5–7 ms appeared to increase the number of counts in the early PSTH peak (from eleven to twenty-one) and decrease the number of counts in the second peak (from thirty-two to thirteen). The net effect was a decrease in the total number of counts (from forty-three to thirty-four).

The ability to stimulate transcallosal pathways in man opens the possibility of investigating changes in activity during voluntary movement. Although we have not investigated this systematically in the present paper, the results suggest that there may be changes in transcallosal excitability accompanying movement of one side of the body. The amount of transcallosal inhibition detected in the relaxed right FDI muscle was increased when subjects voluntarily contracted their left FDI. The effect was small, but quite robust and occurred despite the fact that control responses in the relaxed right FDI were increased in size by activation of the left side. One possible explanation is that contraction of the left FDI is accompanied by activity in transcallosal projections from right to left hemisphere. If so, then transcranial stimulation of the right hemisphere might evoke more callosal inhibition in the left hemisphere. Interestingly, contraction of left FDI had no influence on the amount of transcallosal inhibition when the right FDI was held active throughout the experiment. This may indicate that there is a difference in voluntary control of bilateral *versus* unilateral contraction of hand muscles. Perhaps the callosal connections can, on occasion, operate to inhibit activity in one hand in order to ensure a strictly unilateral movement.

In conclusion, the present experiments have demonstrated that transcranial stimulation in man probably can evoke activity in a transcallosal pathway. The predominant effect appeared to be inhibition, but facilitatory influences, common in animal experiments, may have been underestimated by the techniques we used. The excitability of this inhibitory pathway appears to change during voluntary muscle contraction. One major question arises from these results: how is this powerful inhibitory mechanism overcome in patients with epilepsy whose seizures spread via the corpus callosum?

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## REFERENCES

ASANUMA, H. & OKAMOTO, K. (1959). Unitary study on evoked activity of callosal neurones and its effect on pyramidal tract cell activity on cats. *Japanese Journal of Physiology* **9**, 473–483.

ASANUMA, H. & OKUDA, O. (1962). Effects of transcallosal volleys on pyramidal tract cell activity of cat. *Journal of Neurophysiology* **25**, 198–208.

BERLUCCHI, G. (1990). Commisurotomy studies in animals. In *Handbook of Neuropsychology*, vol. 4, ed. BOLLER, F. & GRAFMAN, J., pp. 9–47. Elsevier, Amsterdam.

BRINKMAN, C. & KUYPERS, H. G. J. M. (1972). Splitbrain monkeys: cerebral control of ipsilateral and contralateral arm, hand and finger movements. *Brain* **176**, 536–539.

BROWN, P., DAY, B. L., ROTHWELL, J. C., THOMPSON, P. D. & MARSDEN, C. D. (1991). Intrahemispheric and interhemispheric spread of cerebral cortical myoclonic activity and its relevance to epilepsy. *Brain* **114**, 2333–2351.

CATSMAN-BERREVOETES, C. E., LEMON, R. N., VANBURGH, C. A., BENTIVOGLIO, M. & KUYPERS, H. G. J. M. (1980). Absence of callosal collaterals derived from rat cortico-spinal neurones. A study using fluorescent retrograde tracing and electrophysiological techniques. *Experimental Brain Research* **39**, 433–440.

CRACCO, R. Q., AMASSIAN, V. E., MACCABEE, P. J. & CRACCO, J. B. (1989). Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. *Electroencephalography and Clinical Neurophysiology* **74**, 417–424.

CRONE, C., HULTBORN, H., MAZIERES, L., MORIN, C., NIELSEN, J. & PIERROT-DESEILLIGNY, E. (1990). Sensitivity of monosynaptic test reflexes to facilitation and inhibition as a function of the text reflex size: a study in man and the cat. *Experimental Brain Research* **81**, 35–45.

CURTIS, H. J. (1940). Intercortical connections of corpus callosum as indicated by evoked potentials. *Journal of Neurophysiology* **3**, 407–413.

DATTA, A. K., HARRISON, L. M. & STEPHENS, J. A. (1989). Task-dependent changes in the size of response to magnetic brain stimulation in human first dorsal interosseous muscles. *Journal of Physiology* **418**, 13–23.

DAY, B. L., DRESSLER, D., MAERTENS DE NOORDHOUT, A., MARSDEN, C. D., NAKASHIMA, K., ROTHWELL, J. C. & THOMPSON, P. D. (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology* **412**, 449–473.

DAY, B. L., RIESCHER, H., STRUPPLER, A., ROTHWELL, J. C. & MARSDEN, C. D. (1991). Changes in the response to magnetic and electric stimulation of the motor cortex following muscle stretch in man. *Journal of Physiology* **433**, 41–58.

DAY, B. L., THOMPSON, P. D., DICK, J. P. R., NAKASHIMA, K. & MARSDEN, C. D. (1987). Different sites of action of electrical and magnetic stimulation of the human brain. *Neuroscience Letters* **75**, 101–106.

DISTEFANO, M., MORELLI, M., MARZI, C. A. & BERLUCCHI, G. (1980). Hemispheric control of unilateral and bilateral movements of proximal and distal parts of the arm as inferred from simple reaction time to lateralised light stimuli in man. *Experimental Brain Research* **38**, 197–204.

EDGLEY, S. A., EYRE, J. A., LEMON, R. N. & MILLER, S. (1990). Excitation of the corticospinal tract by electromagnetic and electrical stimulation of the scalp in the macaque monkey. *Journal of Physiology* **425**, 301–320.

FEENEY, D. M. & OREM, J. M. (1971). Influence of antidromic callosal volleys on single units in visual cortex. *Experimental Neurology* **33**, 310–321.

FERBERT, A., PRIORI, A., ROTHWELL, J. C., COLEBATCH, J. G., DAY, B. L. & MARSDEN, C. D. (1990). Trans-callosal effects on motor cortical excitability in man. *Journal of Physiology* **429**, 38*P*.

GAZZANIGA, M. S. (1963). Effects of commissarotomy on a preoperatively learned visual discrimination. *Experimental Neurology* **8**, 14–19.

GAZZANIGA, M. S. (1969). Cross-cuing mechanisms and ipsilateral eye–hand control in splitbrain monkeys. *Experimental Neurology* **23**, 11–17.

GOULD, H. J., CUSICK, C. G., PONS, T. P. & KAAS, J. H. (1986). The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. *Journal of Comparative Neurology* **247**, 297–325.

HESS, C. W., MILLS, K. R. & MURRAY, N. M. F. (1986). Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. *Neuroscience Letters* **71**, 235–240.

JENNY, J. B. (1979). Commissural projections of the cortical hand motor area in monkeys. *Journal of Comparative Neurology* **188**, 137–146.

JONES, E. G., COULTER, J. D. & WISE, S. P. (1979). The commissural columns in the sensory-motor cortex of monkeys. *Journal of Comparative Neurology*, **188**, 113–135.

KATZ, R., PERICAUD, A. & ROSSI, A. (1991). Reciprocal Ia inhibition between elbow flexors and extensors in the human. *Journal of Physiology* **437**, 269–286.

KERNELL, D. & WU, C.-P. (1967). Responses of the pyramidal tract to stimulation of the baboon's motor cortex. *Journal of Physiology* **191**, 653–672.

MATSUNAMI, K. & HAMADA, I. (1984). Effects of stimulation of corpus callosum on precentral neuron activity in the awake monkey. *Journal of Neurophysiology* **52**, 676–691.

NAKAMURA, K., NAITO, H., MUROSAKI, T. & TAMURA, Y. (1971). Effects of polarising currents on transcallosal post-synaptic potentials of cat pyramidal tract cells. *Brain Research* **35**, 547–550.

PAPPAS, C. L. & STRICK, P. L. (1981). Anatomical demonstration of multiple representation in the forelimb region of the cat motor cortex. *Journal of Comparative Neurology* **200**, 491–500.

PURPURA, D. P. & GIRADO, M. (1959). Synaptic mechanisms involved in transcallosal activation of cortico-spinal neurones. *Archives Italiennes des Biologie* **47**, 111–139.

REEVES, A. G. (1985). *Epilepsy and the Corpus Callosum.* Plenum Press, New York.

ROSSINI, P. M., CARAMIA, M. D. & ZAROLA, F. (1987). Mechanisms of nervous propagation along central motor pathways: noninvasive evaluation in healthy subjects and in patients with neurological disease. *Neurosurgery* **20**, 183–191.

ROTHWELL, J. C., COLEBATCH, J. G., BRITTON, T. C., PRIORI, A., THOMPSON, P. D., DAY, B. L. & MARSDEN, C. D. (1991). Physiological studies in a patient with mirror movements and agenesis of the corpus callosum. *Journal of Physiology* **438**, 34*P*.

SARON, C. D. & DAVIDSON, R. J. (1989). Visual evoked potential measures of interhemispheric transfer time in humans. *Behavioral Neuroscience* **103**, 1115–1138.

SCHIEPPATI, M., MUSAZZI, M., NARDONE, A. & SEVESO, G. (1984). Interhemispheric transfer of voluntary motor commands in man. *Electroencephalography and Clinical Neurophysiology* **57**, 441–447.

SCHRIEFER, T. N., MILLS, K. R., MURRAY, N. M. F. & HESS, C. W. (1988). Evaluation of proximal facial nerve conduction by transcranial magnetic stimulation. *Journal of Neurology, Neurosurgery and Psychiatry* **51**, 60–66.

SHIBASAKI, H., YAMASHITA, Y. & KUROIWA, J. (1978). Electroencephalographic studies of myoclonus. *Brain*, **101**, 447–460.

SPERRY, R. W. (1974). Lateral specialisation in the surgically separated hemispheres. In *The Neurosciences Third Study Program*, ed. SCHMITT, F. O. & WORDEN, F. G., pp. 5–19. MIT Press, Cambridge, MA, USA.

SPIDALIERI, G., GUANDALINI, P. & FRANCHI, G. (1986). Motor responses mediated by orthodromic and antidromic activation of the rostral portion of the cat corpus callosum. *Experimental Brain Research* **64**, 133–142.

TOMASCH, J. (1954). Size, distribution and number of fibres in the human corpus callosum. *Anatomical Record* **119**, 119–135.

UGAWA, Y., DAY, B. L., ROTHWELL, J. C., THOMPSON, P. D., MERTON, P. A. & MARSDEN, C. D. (1991). Modulation of motor cortical excitability by electrical stimulation over the cerebellum in intact man. *Journal of Physiology* **441**, 57–72.

WASSERMAN, E. M., FUHR, P., COHEN, L. G. & HALLETT, M. (1990). Effects of transcranial magnetic stimulation on ipsilateral muscles in humans. *Society for Neuroscience Abstracts* **16**, 243.

WILKINS, D. E., HALLETT, M., BERARDELLI, A., WALSHE, T. & ALVAREZ, N. (1984). Physiologic analysis of the myoclonus of Alzheimer's disease. *Neurology* **34**, 898–903.