# The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex

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1. It has been previously shown that in a relaxed target muscle, at short interstimulus intervals (ISIs) (up to 6 ms) a conditioning subthreshold transcranial magnetic stimulus can cause suppression of the EMG response evoked by a magnetic test stimulus. At longer ISIs (7–15 ms) facilitation of the test response is seen. This type of inhibition has been termed ipsilateral cortico-cortical inhibition.

2. The effect of a minimal tonic contraction on ipsilateral cortico-cortical inhibition has been investigated in the first dorsal interrosseous (FDI).

3. At short ISIs there was significantly less inhibition of the test response during the maintenance of minimal voluntary tonic contraction of the target muscle (FDI).

4. At longer ISIs (7–15 ms) there was significantly less facilitation of the test response during a tonic contraction than during relaxation.

5. Minimal activation of an ipsilateral proximal muscle (biceps) had no significant effect on the degree of inhibition seen in the relaxed target muscle (FDI).

6. We suggest that voluntary drive reduces the excitability of inhibitory circuits in cortical areas that project to the active muscle.

If two magnetic stimuli are given to the motor cortex through the same coil, EMG responses evoked in small hand muscles by the second stimulus can be suppressed by the first conditioning stimulus when (i) the intensity of the conditioning shock is below threshold for producing responses in relaxed muscle, and (ii) the interval between the conditioning and test stimuli is short (< 6 ms; Kujirai *et al.* 1993). We have argued that the effect occurs because of inhibitory interactions at a cortical level. If this is so, the technique is a means of monitoring the excitability of intracortical circuitry in conscious man. In previous experiments the excitability of this circuitry was evaluated with the subject at rest. The aim of the present experiments was to examine whether the excitability of the system changes during performance of different voluntary movements. The changes we have observed are the first demonstration that the operation of cortico-cortical circuits changes during movement in conscious man.

An abstract of some of these results has been published previously (Ridding, Taylor & Rothwell, 1993).

## METHODS

A total of fourteen normal subjects were studied, all of whom gave informed consent, and the procedures were approved by the local ethical committee. Six individuals participated in the main set of experiments. They consisted of one female and five males with ages ranging from 30–47 years (mean 35·3 ± 6 years). EMGs were recorded from the first dorsal interosseous (FDI) muscle using 0·9 cm diameter Ag–AgCl surface electrodes with the active electrode placed over the muscle belly and the reference electrode over the interphalangeal joint. Magnetic stimuli were applied over the motor cortex through a figure-of-eight coil (external wing diameters 9 cm) powered by two magnetic stimulators (High Power Magstim 200) linked with a Bistim unit (Magstim, Dyfed, UK). This device allows two magnetic stimulators to discharge through the same coil but reduces the maximum power output by about 30%. Thus, the maximum peak magnetic field delivered by the figure-of-eight coil after a single shock is 1·5$T$ rather than 2·2$T$ which is delivered when the same coil is connected directly to a Magstim unit. In the text, stimulus intensities are expressed as a percentage of the maximum stimulator output when connected via the Bistim unit. The stimulating coil was placed over the optimal site for eliciting responses in the target muscle (FDI) and oriented so that the current induced in the brain flowed in a posterior–anterior direction through this optimal stimulating site. Electromyographic (EMG) responses were amplified, using two channels with gains of 100 $\mu$V V$^{-1}$ and 1 mV V$^{-1}$, and filtered (high frequency (HF) filter, 3 kHz; time constant (TC), 3 ms) before being sampled (5 kHz per channel) and stored, by means of a CED 1401 interface (Cambridge Electronic Design, Cambridge, UK) linked to a PC, for later analysis.

The magnetic stimulation threshold for eliciting responses in the FDI muscle was determined in both the relaxed and voluntarily

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active states. Subjects were given audio-visual feedback of EMG activity to assist in maintaining either complete relaxation or the correct amount of activation. Threshold was determined using the high gain channel, and was defined as being the intensity of stimulation needed to produce responses of 25–30 $\mu$V in at least 50% of successive trials. For the determination of active threshold, subjects were instructed to maintain a tonic contraction of approximately 5% of their maximum voluntary contraction (MVC), and were given an EMG level indicator on an oscilloscope in order to assist them in maintaining the correct level of activation.

Cortical inhibition was evaluated using paired magnetic stimuli as described by Kujirai *et al.* (1993). Briefly, two magnetic stimuli were given through the figure-of-eight coil held over the motor cortex. The first (conditioning) stimulus was set at an intensity 5% (of stimulator output) below the threshold for producing responses in minimally active (5% MVC) FDI. The second (test) stimulus was set at an intensity such that when it was given alone, it could evoke an EMG response of approximately 1 mV peak-to-peak amplitude. Applying this criterion to both active and relaxed conditions meant that slightly lower intensities of test shock were used when subjects were active than when they were relaxed. The timing of the conditioning stimulus was altered in relation to that of the test shock. Interstimulus intervals (ISIs) of 1–15 ms were investigated. Six blocks of forty trials were recorded in each subject, three in the relaxed state and three in the active state. Each block consisted of four different conditions; test stimulus alone and test + conditioning stimuli at three different ISIs. The order of presentation of these four conditions was generated pseudo-randomly by the computer. Measurements were made on individual responses and the area of the conditioned response, at each ISI, was expressed as a percentage of the area of the response to the test shock given alone.

In eight subjects (3 female, 5 male; mean age, 28 ± 2·9 years) we assessed the effect of distant muscle activation on the level of ipsilateral cortico-cortical inhibition in the relaxed FDI. Subjects maintained a minimal (5%) tonic contraction of the ipsilateral biceps muscle while keeping FDI relaxed, and ipsilateral cortico-cortical inhibition was measured as described above. ISIs of 1, 2 and 3 ms were investigated. Visual feedback of the EMG level (using the high gain channel) was given to the subjects, via an oscilloscope, to assist in the maintenance of a consistent level of contraction. The test intensity was the same as that in the main set of experiments (sufficient to evoke an EMG response of approximately 1 mV) and the conditioning intensity was set at an intensity 5% of stimulator output below the threshold for evoking responses in the tonically active FDI.

A number of control experiments were performed using a variety of conditioning and test shock intensities. As in the main set of experiments FDI was the muscle studied. In the first of these experiments six subjects (2 female, 4 male; mean age, 26 ± 3·7 years) were studied at rest, using similar methods to those already described. Three inhibitory ISIs were used (1, 2 and 3 ms) and the degree of suppression of the test response was investigated at each of these different ISIs with varying test stimulus intensities. In each subject, the test stimulus was adjusted so as to evoke small (amplitude range, 0·3–1 mV) and large (2–4 mV) test responses. The second set of experiments was performed on three subjects (3 males; mean age, 37 ± 10 years). In these experiments the difference in the suppression of the test response when subjects were active or relaxed was compared (a) in the standard way, in which the size of the test shock was adjusted to produce responses of equal size in the two conditions, and (b) when the size of the test shock was constant in the two conditions. In the latter case, the test responses were larger than our standard 1 mV peak to peak. ISIs of 2, 3 and 4 ms were investigated. The conditioning intensity was set at 5% of stimulator output below the active threshold (as in the main set of experiments). In the third set of experiments two subjects were studied and the effect of varying the conditioning intensity while keeping the test intensity constant was investigated. This was done with the target muscle (FDI) both relaxed and active. For these experiments ISIs of 1, 2, 3, 4, 7 and 10 ms were investigated. The conditioning stimulus was set at an intensity ranging from active threshold to 30% of stimulator output below active threshold.

### Statistics

For the controls and the main set of experiments the results were analysed using repeated measures analysis of variance. Student's paired $t$ test was used in the main set of experiments to compare the results obtained in the active and relaxed conditions at individual ISIs. Unless otherwise stated data are given as means ± S.D.

## RESULTS

### Comparison of paired-pulse effects in relaxed *versus* active FDI

These experiments were performed on the main group of six subjects. The mean conditioning intensity was 38 ± 8% of the maximum stimulator output delivered via the Bistim unit (see Methods). The intensity of the test shock averaged 79 ± 19% in the relaxed condition, but was reduced to 52 ± 11% when the subjects were active.

Figure 1*A* is an example of the effect of voluntary contraction on paired-pulse effects in a single subject. Traces show EMG responses in FDI to the test stimulus given alone and when conditioned by a subthreshold shock given 2 ms earlier. When the subject was relaxed, the test shock given alone produced a response which was approximately 1·0 mV peak-to-peak amplitude. This was suppressed to 0·2 mV when conditioned at an ISI of 2 ms. When the subject was active, the test shock was adjusted so that it evoked an EMG response which was about 1·4 mV peak to peak. However, the conditioning stimulus (which was the same intensity as when relaxed) now had little effect.

The time course in Fig. 1*B* illustrates the mean data for all six subjects. When relaxed, the conditioning stimulus suppressed test responses at intervals of 1–5 ms, and enhanced them at 10 and 15 ms. When active, the time course was 'flattened', i.e. there was less suppression and less facilitation. For analysis of the time course the ISIs were divided into two groups: 1–5 ms and 6–15 ms. This was done because of the limited number of subjects in this set of experiments. This analysis revealed a significant ($F(1,5)$, 21·35; $P < 0·05$) state (active/relaxed) by ISI interaction. Individual paired $t$ tests revealed that during

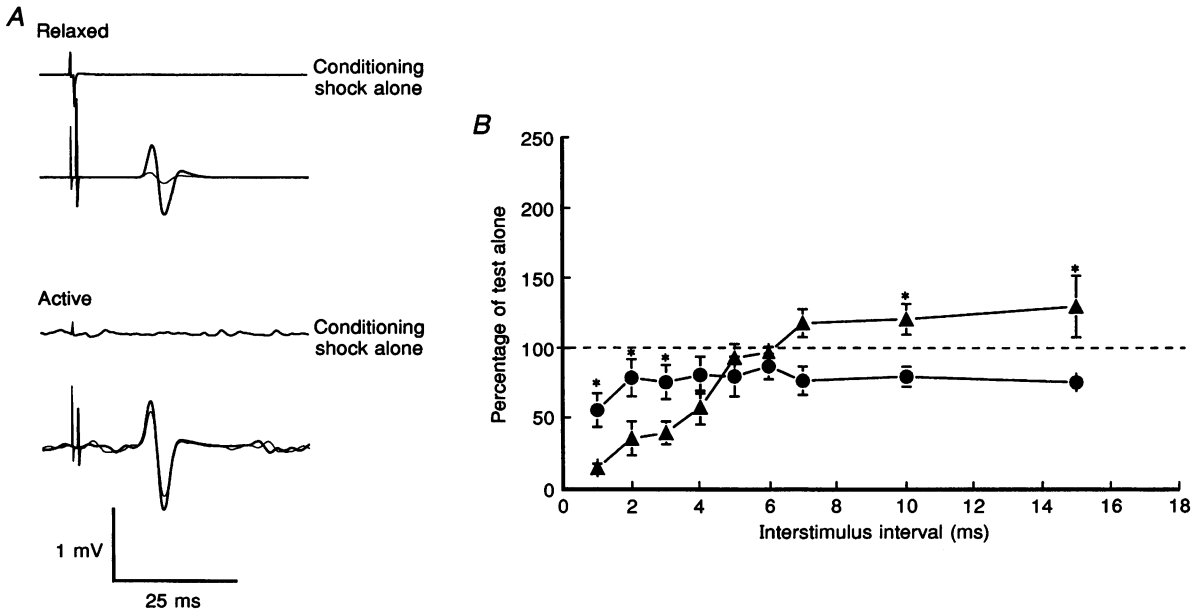


**Figure 1. The effect of voluntary contraction on paired-pulse inhibition**

*A*, raw data showing effect of voluntary contraction upon paired-pulse inhibition recorded in FDI at an ISI of 2 ms. Each trace represents the mean response of ten trials. For each pair of traces, the upper record shows the absence of any EMG response to the conditioning shock given alone; the lower record shows the response to the test shock given alone (thick trace) superimposed on the response to the conditioning + test stimuli (thin trace). The conditioning intensity was the same in both the active and relaxed conditions and was set at 5% below the threshold for evoking responses in active FDI. The test intensity was set to give a test response in the active state that was similar in size to the one evoked when the target muscle was relaxed. When FDI is activated there is much less inhibition of the test response. *B*, time course of paired-pulse inhibition during both relaxation (▲) and a minimal tonic contraction of FDI (●). Each point represents the mean value from six subjects, bars indicate S.D. The abcissa indicates the ISIs studied and the ordinate the area of the conditioned response as a percentage of the test response alone. It can be seen that over short ISIs (1–5 ms) there is less inhibition when the target muscle is active compared with the relaxed state. Also, at long ISIs, there is less facilitation when active compared with relaxed (* $P < 0{\cdot}05$, paired $t$ test).

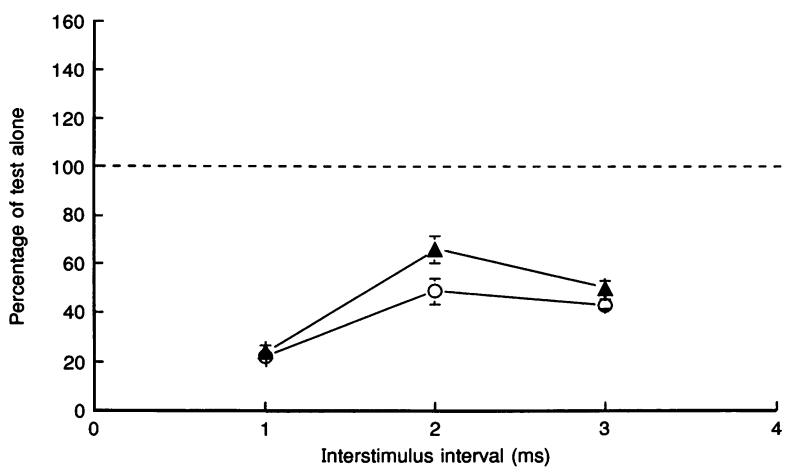


**Figure 2. Effect of proximal muscle contraction on paired-pulse inhibition**

The effect of mild (5% MVC) voluntary contraction of the (ipsilateral) biceps muscle (○) on paired-pulse inhibition in relaxed FDI (▲). Mean data (± S.E.M.) from 8 subjects. The abcissa indicates the ISIs studied and the ordinate represents the area of the conditioned response, expressed as a percentage of the response to the test shock given alone.

activation, there was a significant reduction ($P < 0{\cdot}05$) in suppression at intervals of 1, 2 and 3 ms and reduced facilitation at 10 and 15 ms. In this study we did not investigate the precise onset of the inhibitory effect. Because of interaction between the two stimulators it is not possible to study ISIs of less than 1 ms. However, from previous work (Kujirai *et al.* 1993) it appears as though the effect is not evident when the conditioning stimulus is applied 1 ms later than the test stimulus (i.e. ISI = −1 ms)

### Effect of biceps contraction on paired-pulse inhibitory effects in FDI

In eight subjects we tested the effect of weak biceps (5% MVC) muscle contraction on paired-pulse inhibition in FDI. With the aid of auditory and visual feedback, subjects maintained relaxation of FDI throughout the experiment. Intervals of 1, 2 and 3 ms between conditioning and test stimuli were examined since they had shown the greatest changes during contraction of FDI itself. Figure 2 illustrates that inhibition in FDI was the same whether biceps was relaxed or tonically active when considering intervals of 1–3 ms ($F(1,7)$, 2·12; $P > 0{\cdot}05$).

### Effect of test shock intensity on paired-pulse inhibition

In the experiments above, the intensity of the test shock was adjusted to produce control EMG responses of approximately the same size when subjects were active or relaxed. The following experiments were performed to examine what effect varying the test response size had on the percentage inhibition produced by a constant conditioning shock.

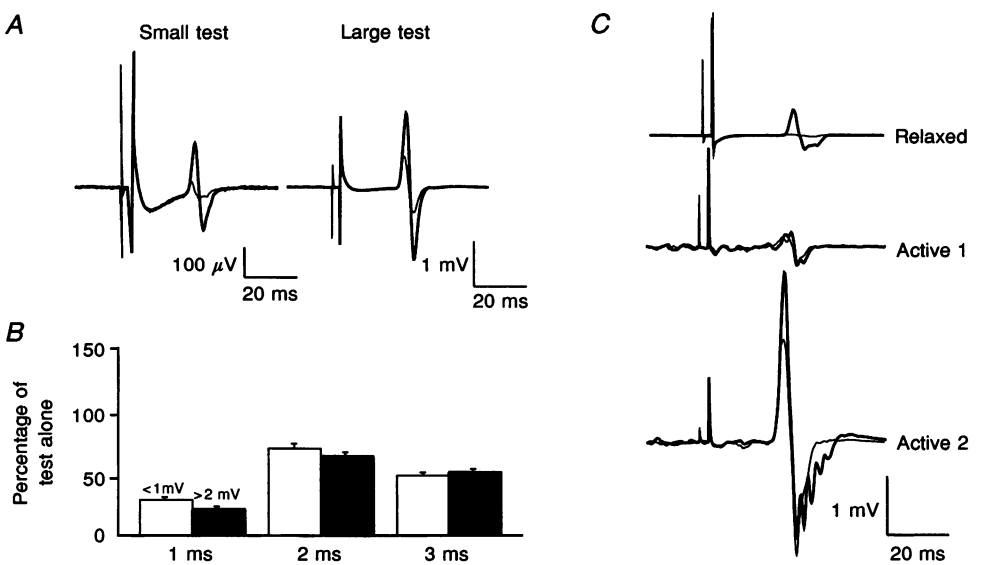


**Figure 3. Effect of changing the size of the test shock on the amount of paired-pulse inhibition**

The left-hand panels (*A* and *B*) refer to data collected when subjects were at rest. *A*, raw data from a single subject. The superimposed EMG responses from FDI illustrate the size of the response to a test shock given alone (thick trace) and the response when conditioned by a conditioning shock given 3 ms earlier (thin trace). In both cases the conditioning intensity is the same and was set at 5% below the threshold for evoking responses in active FDI. Two different test intensities were employed which resulted in test responses of 300 μV (left trace) and 3·4 mV (right trace; note calibration) being evoked. There was no difference in the percentage inhibition with the two sizes of test response. Area ratio for both was 0·16. *B*, mean (+ S.E.M.) data from six subjects. Three different ISI were investigated (1, 2 and 3 ms). □, results when the peak-to-peak amplitude of the mean test response was less than 1 mV. ■, results when the test response was larger than 2 mV. The ordinate indicates the area of the conditioned response as a percentage of the test response alone. Across these three ISIs there was no significant difference in the degree of inhibition with the different test response sizes ($P > 0{\cdot}05$). *C*, raw data from one subject showing the effect of varying the test intensity in the active condition. The intensity of the conditioning shock was constant throughout. The top pair of traces shows that in relaxed muscle, the test response (thick line) is almost completely suppressed when preceded by a conditioning stimulus given 3 ms earlier (thin trace). In the middle pair of traces (Active 1) the target muscle was active and the test intensity reduced so as to evoke an EMG response equal in size to that evoked in relaxed muscle (top traces). In this condition there was minimal inhibition of the test response. In the bottom pair of traces (Active 2) the test intensity was the same as that used when the target muscle was relaxed. This resulted in a test response of much greater amplitude than in the relaxed state. With this size of test response, again, there was only minimal inhibition.

**Relaxed muscle.** For relaxed muscle, the size of test response had no effect on the inhibition. The six (younger) subjects who participated in this series of trials had slightly lower mean thresholds (relaxed, 47 ± 6%; active, 35 ± 6%; via Bistim) than the initial group who were compared when active and relaxed. In each subject, the conditioning intensity was kept constant (30 ± 6%; via Bistim), whilst ISIs of 1–3 ms were investigated. In separate blocks of trials, two intensities of test shock were used in order to evoke EMG responses which lay within two broad amplitude ranges, 0·3–1·0 mV or 2·0–4·0 mV (mean test intensity, 53 ± 6 and 60 ± 10%, respectively; via Bistim). Figure 3*A* and *B* shows that the conditioning stimulus produced the same percentage suppression for both sizes of test response ($F(1,7)$, 0·45; $P > 0·5$).

**Active muscle.** Again, the size of the test response did not alter the paired-pulse inhibition. In our initial experiments, we reduced the intensity of the test stimulus when subjects were active so that it evoked an EMG response within our standard range 1–2 mV peak-to-peak amplitude. In three subjects we measured the amount of inhibition using a test stimulus of equal intensity to that employed in the relaxed state. With the target muscle relaxed the test response had an amplitude of 1·2 ± 0·53 mV for the three subjects. In the active state with the usual (lower) intensity of test stimulus the test response had an amplitude of 0·97 ± 0·25 mV, and with the higher test intensity (the same as that used when relaxed) an amplitude of 4·0 ± 0·66 mV. In the relaxed muscle, responses were suppressed to an average of 28 ± 1% of the test response alone. When the muscle was active, using the lower test intensity, responses were 83 ± 24% of the test alone. With activity and using the higher test intensity, responses were 100 ± 21% of the test response. The percentage inhibition was not significantly different at any of the ISIs studied (2, 3 and 4 ms) in the two active conditions ($P > 0·05$). An example from one of the subjects is shown in Fig. 3*C*.

### Effect of conditioning shock intensity

Figure 4 shows the effect, in three subjects, of varying the intensity of the conditioning shock using a conditioning–test interval of 3 ms. When subjects were relaxed there was good suppression of the test response if the conditioning intensity was between active threshold and approximately 10% of stimulator output below active threshold. However, inhibition was still evident at 20% below active threshold. When the subjects were active, conditioning stimuli produced only minimal suppression of the test response. This was maximal, as in the relaxed state, when the conditioning intensity was set at approximately 10% below active threshold. Similar effects were observed at different conditioning–test intervals. The time course of paired-pulse suppression using different intensities of conditioning shock can be seen in Fig. 5*A* and *B*, representing data obtained in two subjects. Figure 5*A* shows the effect in relaxed FDI, while Fig. 5*B* shows the effect in tonically active FDI. In both cases, maximum suppression is seen with conditioning stimuli which were 5–10% of stimulator output below active threshold.

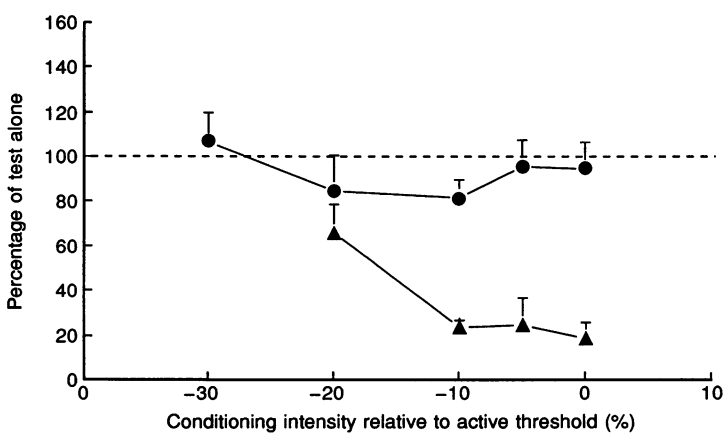


**Figure 4. The effect of conditioning intensity on paired-pulse inhibition**

The effect of varying conditioning intensity on paired-pulse inhibition in both relaxed (▲) and active (●) FDI at an ISI of 3 ms. Each point represents the mean value (+ S.E.M.) of inhibition for three subjects. The abscissa indicates the conditioning intensity used, expressed in percent of stimulator output below or above active threshold. Active threshold was defined as 0%. The ordinate indicates the size of the conditioned response, expressed as a percentage of the test response alone. It can be seen that for relaxed FDI inhibition is maximal over a range from active threshold to approximately 10% below active threshold. In the active state, inhibition is minimal across the whole range, but reaches its maximal level at approximately 10% of stimulator output below active threshold.

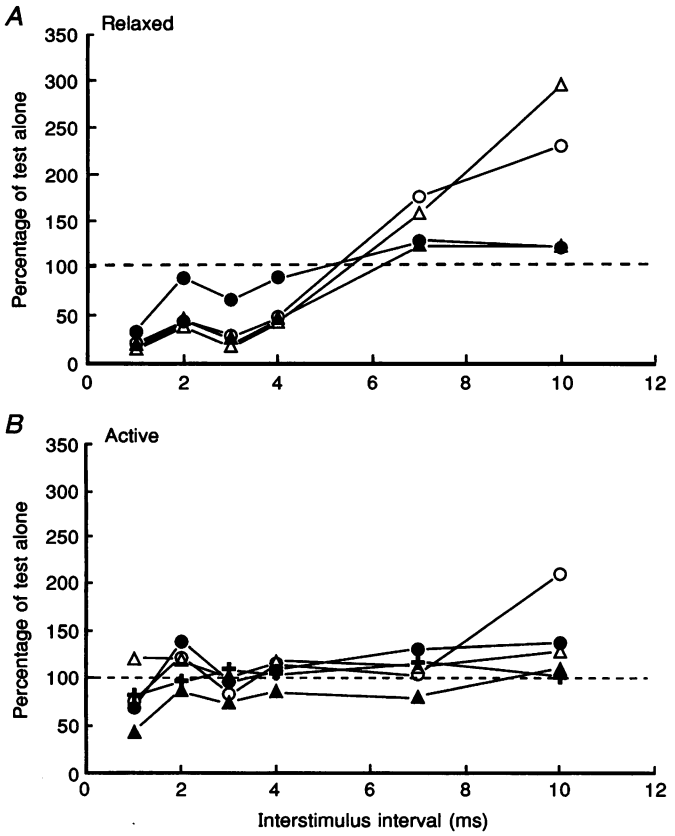


**Figure 5. The effect of varying conditioning shock intensity on paired-pulse inhibition across a range of ISIs, in relaxed FDI and active FDI**

Each point represents the mean data from 2 subjects. In the relaxed state (*A*) the conditioning intensity was varied from active threshold (△) to 5 (○), 10 (▲) and 20% (of stimulator output) below active threshold (●), and in the active state (*B*) the conditioning intensity was varied from active threshold (△) to 5 (○), 10 (▲), 20 (●) and 30% (+) (of stimulator output) below active threshold. The abscissa indicates the ISIs and the ordinate the size of the conditioned response, expressed as a percentage of test response alone.

## DISCUSSION

We have demonstrated that suppression, at short intervals, of a magnetically evoked test response by a subthreshold conditioning stimulus, is reduced during the maintenance of a minimal tonic contraction. We have argued previously that this inhibition is cortical in nature, mainly for the following three reasons. (1) During a tonic contraction many spinal motoneurones are near their firing thresholds and if the conditioning stimulus produced a descending volley, we would expect this volley to discharge some of the motoneurones leading to an EMG response being evoked in the target muscle. Conditioning stimuli of the intensity used for these experiments are, in fact, well below threshold for producing responses in active muscles. We assume, therefore, that the conditioning stimulus produces very little or no descending activity in the corticospinal tract. (2) Conditioning stimuli of this intensity have no inhibitory effect on spinal H reflexes (Kujirai *et al.* 1993) even though they produce good suppression of the EMG response to magnetic stimulation of the cortex. (3) If electrical test stimuli are used to activate the cortex instead of magnetic test stimuli then conditioning stimuli of this intensity produce much less inhibition of the test response (Kujirai *et al.* 1993). This is explained in the following way. Anodal electrical stimulation at low intensities tends to activate the axons of the corticospinal tract in the white matter, whilst magnetic stimulation tends to activate either at the level of the initial segment or transynaptically within the cortex (Rothwell, Thompson, Day, Boyd & Marsden, 1991). As both forms of stimulation are thought to use the same descending fibres (Edgley, Eyre, Lemon & Miller 1991) it appears likely that the suppressive effect of magnetic stimulation is caused by activation of cortical inhibitory mechanisms.

A final piece of evidence that the suppression we have studied occurs because of activity of cortical inhibitory circuits comes from results in neurological patients. We have been able to demonstrate reduced paired-pulse suppression in patients with cortical myoclonus (Ridding, Brown & Rothwell, 1994). In these patients the pathology is in the cortex and we suggest that the reduced inhibition is a reflection of alterations in the efficacy of intracortical actions, and may be partly responsible for the generation and spread of their myoclonic jerks. In this study we have not investigated the onset of the inhibitory effect.

### Effect of changing the intensity of the test or conditioning shock

When the target muscle was active, lower intensities were used for the test stimulus in comparison with the relaxed state. This was done in order to match the size of the evoked EMG responses. It was possible that this difference in stimulating intensity might have been the reason for the observed difference in levels of inhibition between the two

states. We think this unlikely since the amount of inhibition was fairly consistent across a wide range of response amplitudes, at least in relaxed muscle. In addition, when we did use the same test intensity in both the active and relaxed conditions, there was no significant increase in the amount of inhibition during voluntary contraction.

In most experiments, the intensity of the conditioning shock was kept constant. However, this does not guarantee that the same population of cortical neurones was activated in the relaxed and active states. The threshold for transcranial stimulation of cortex is decreased during voluntary activity (Mazzocchio, Rothwell, Day & Thompson, 1994) so that a constant conditioning stimulus may have activated a larger population of neurones than at rest. If so, this may have affected the amount by which the test response was suppressed. This seems unlikely to account for our findings, as changing the intensity of the conditioning stimulus demonstrated that at all intensities the amount of suppression was less when active than when relaxed.

### Effect of proximal muscle contraction

Although we observed large changes in the amount of cortical suppression during contraction of the target muscle (FDI), contraction of a remote muscle (biceps) had no significant effect. This indicates that the changes we observed were specific for the muscle studied and not simply the result of changing the task required of the subject. Indeed, since there was a slight increase in the amount of suppression during biceps contraction at all intervals tested, it may even be that contraction of remote muscles might facilitate cortical inhibition onto the target muscle. Whether this would be evident during contraction of muscles closer to the target requires further investigation.

### Is the reduction in paired-pulse inhibition during voluntary activity due to changes in the excitability of cortical circuits?

Our results show that there is less paired-pulse inhibition when subjects are active compared with at rest. We have argued that this inhibition is likely to be of cortical origin. The question remains as to whether a decrease in the amount of inhibition is due to changes in excitability at cortical or subcortical levels. In particular, could the conditioning stimulus cause spinal level facilitation when active but not when relaxed, and hence partly compensate for an inhibited corticospinal volley? It is not possible to study H reflexes in the FDI muscle in order to investigate the effect of a subthreshold conditioning stimulus on spinal cord excitability but there are two reasons for rejecting this suggestion. First, it seems improbable that a stimulus intensity of 5% (of the stimulator output) below the threshold for evoking EMG responses in active muscle could produce any descending corticospinal activity. Second, if a minimal volley were responsible for producing spinal facilitation, then it should have been possible to increase the intensity of the conditioning stimulus when subjects were relaxed and obtain a similar decrease in paired-pulse inhibition. This was not the case: at rest, conditioning stimuli at an intensity as high as active motor threshold produced good inhibition which was no less than that seen with intensities of 15% (of stimulator output) lower. We conclude that the reduced paired-pulse inhibition observed during voluntary activity is due to changes in excitability of cortical circuits. It is impossible to be certain whether voluntary contraction produces a decrease in excitability of inhibitory circuits or a concurrent increase in excitability of facilitatory circuits. However, there is one observation that leads us to favour the former possibility. Paired-pulse testing at rest revealed facilitation at longer ISIs (10 and 15 ms), which was absent during activity. Thus, there was no evidence in the present data for increased facilitation and hence we suggest that the decreased paired-pulse inhibition during activity is likely to be caused by a reduction in excitability of cortical inhibitory circuits.

At these later ISIs, the reduction in the level of facilitation of the test response during voluntary activity was significant at 10 and 15 ms. At the present time we are unsure of the mechanism of this later facilitation, and hence would like to keep the discussion directed primarily to the alterations in inhibition. Nevertheless, it would not be surprising if voluntary contraction had effects on intracortical circuits other than those responsible for the initial suppression. However, further studies would be needed to tease these factors apart.

### Comparison with previous work

It is known that transcranial stimulation over the motor cortex at intensities less than the threshold for evoking an EMG response can produce a short period of silence in the EMG of tonically active muscle (Calancie, Nordin, Wallin & Hagbarth 1987; Davey, Romaiguere, Maskill & Ellaway 1992; Davey, Romaiguere, Maskill & Ellaway 1994). In a previous paper (Kujirai *et al.* 1993) we compared the inhibition revealed with paired-pulse testing at rest with low threshold inhibition of on-going EMG and concluded that since the threshold for the effects was similar, they may share some common mechanisms. However, there were two points of difference between the techniques: the amount of suppression with paired-pulse testing at rest was shorter, but much deeper than the suppression of on-going voluntary EMG (Davey *et al.* 1994). The present results with paired-pulse testing during voluntary activity help resolve the discrepancies. During contraction, paired-pulse testing results in less suppression, which lasts longer (suppression to approximately 80% seen at all ISIs tested from 1–15 ms) than when at rest. It seems likely that during tonic voluntary contraction, the effect of a single submotor threshold conditioning shock on both a subsequent larger test shock or on the on-going EMG in a muscle may be due to activity in similar cortical inhibitory circuits. Further support for this conclusion would necessitate comparison of the complete time course of effects in both cases.

### Relevance of present results

We suggest that the suppression of test responses that we record with this double stimulus technique is caused by activity in local intracortical inhibitory neurones. Why should the excitability of these circuits be decreased during voluntary contraction? We speculate that during a voluntary contraction it may be important to 'switch off' or downregulate the action of inhibitory neurones which project onto populations of corticomotoneuronal cells involved in the intended movement. This would increase the excitability of the 'muscle field' in the cortex and hence facilitate the movement. The reduction in cortico-cortical inhibition demonstrated in these experiments may be a reflection of this downregulation and may be a means of examining dynamic modulation of cortical circuitry during different tasks. Such modulation may be related to the longer-term changes in excitability of cortical inhibitory circuits which are thought to be responsible for reorganization of cortical motor maps following peripheral injury (Donoghue & Sanes 1988; Cohen, Bandinelli, Findlay & Hallett, 1991) or after anaesthetic or ischaemic block of a limb (Brasil-Neto *et al.* 1993).

BRASIL-NETO, J. P., VALLS-SOLE, J., PASCUAL-LEONE, A., CAMMAROTA, A., AMASSIAN, V. E., CRACCO, R., MACCABEE, P., CRACCO, J., HALLETT, M. & COHEN, L. G. (1993). Rapid modulation of human cortical motor outputs following ischaemic nerve blocks. *Brain* **116**, 511–525.

CALANCIE, B., NORDIN, M., WALLIN, U. & HAGBARTH, K. (1987). Motor-unit responses in human wrist flexor and extensor muscles to transcranial cortical stimuli. *Journal of Neurophysiology* **58**, 1168–1185.

COHEN, L. G., BANDINELLI, S., FINDLAY, T. W. & HALLETT, M. (1991). Motor reorganisation after upper limb amputation in man. *Brain* **114**, 615–627.

DAVEY, N. J., ROMAIGUERE, P., MASKILL, D. W. & ELLAWAY, P. H. (1992). Inhibition of voluntary contraction by transcranial magnetic stimulation of the brain subthreshold for excitation in man. *Journal of Physiology* **446**, 447*P*.

DAVEY, N. J., ROMAIGUERE, P., MASKILL, D. W. & ELLAWAY, P. H. (1994). Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. *Journal of Physiology* **477**, 223–235.

DONOGHUE, J. P. & SANES, J. N. (1988). Organisation of adult motor cortex representation patterns following neonatal forelimb nerve injury in rats. *Journal of Neuroscience* **8**, 3221–3232.

KUJIRAI, T., CARAMIA, M. D., ROTHWELL, J. C., DAY, B. L., THOMPSON, P. D., FERBERT, A., WROE, S., ASSELMAN, P. & MARSDEN, C. D. (1993). Cortico-cortical inhibition in human motor cortex. *Journal of Physiology* **471**, 501–520.

EDGLEY, S. A., EYRE, J. A., LEMON, R. N. & MILLER, S. (1991). Direct and indirect activation of corticospinal neurones by electrical and magnetic stimulation in the anaesthetized macaque monkey. *Journal of Physiology* **446**, 224*P*.

MAZZOCCHIO, R., ROTHWELL, J. C., DAY, B. L. & THOMPSON, P. D. (1994). Effect of voluntary activity on the excitability of human motor cortex. *Journal of Physiology* **474**, 261–267.

RIDDING, M. C., TAYLOR, J. & ROTHWELL, J. C. (1993). The effect of voluntary contraction on cortico-cortical inhibition in the cortical motor areas of man. *Society for Neuroscience Abstracts* **19**, 1205.

RIDDING, M. C., BROWN, P. & ROTHWELL, J. C. (1994). Ipsilateral cortico-cortical inhibition in patients with cortical myoclonus. *Movement Disorders* **9**, suppl. 2, 138.

ROTHWELL, J. C., THOMPSON, P. D., DAY B. L., BOYD, S. & MARSDEN, C. D. (1991). Stimulation of the human motor cortex through the scalp. *Experimental Physiology* **76**, 159–200.

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