Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man

Nick J. Davey, Patricia Romaiguère, David W. Maskill and Peter H. Ellaway

Department of Physiology, Charing Cross and Westminster Medical School, Fulham Palace Road, London W6 8RF

1. Suppression of voluntary muscle activity of hand and arm muscles in response to transcranial magnetic stimulation (TMS) of the motor cortex has been investigated in man.

2. Suppression could be elicited by low levels of TMS without any prior excitatory response. The latency of the suppression was 3–8 ms longer than the excitation observed at a higher stimulus intensity. The duration of the suppression ranged from 8 to 26 ms.

3. A circular stimulating coil was used to determine threshold intensity for excitation and suppression of contraction of thenar muscles in response to TMS at different locations over the motor cortex. The locations for lowest threshold excitation coincided with those for lowest threshold suppression. Suppression was elicited at a lower threshold than excitation at all locations.

4. A figure-of-eight stimulating coil was positioned over the left motor cortex at the lowest threshold point for excitation of the right thenar muscles. The orientation for the lowest threshold excitatory and inhibitory responses was the same for all subjects. That orientation induced a stimulating current travelling in an antero-medial direction. Suppression was invariably elicited at lower thresholds than excitation.

5. When antagonistic muscles (second and third dorsal interosseus) were co-contracted, TMS evoked coincident suppression of voluntary EMG in the two muscles without prior excitation of either muscle. This suggests that the suppression is not mediated via corticospinal activation of spinal interneurones.

6. Test responses to electrical stimulation of the cervical spinal cord were evoked in both relaxed and activated thenar muscles. In the relaxed muscle, prior TMS at an intensity that would suppress voluntary activity failed to influence the test responses, suggesting absence of inhibition at a spinal level. However, in the activated muscle, prior TMS could reduce the test response. This may be explained by disfacilitation of motoneurones due to inhibition of corticospinal output.

7. We propose that suppression of voluntary muscle activity by TMS is due in large part to activation of a mechanism within the motor cortex that reduces the corticospinal output to the muscle. It is concluded that TMS evokes excitation and inhibition via neuronal structures lying close to one another and having similar orientations.

The initial excitatory response in skeletal muscles evoked by an anodal transcranial electrical stimulus (Merton & Morton, 1980) applied to the motor cortex is thought to occur as a result of direct excitation of corticospinal axons (Day *et al.* 1989*a*). This is not the case with transcranial magnetic stimulation (TMS) (Barker, Jalinous & Freeston, 1985). The longer latency and greater ease with which responses to TMS can be facilitated led to the proposal (Rothwell, Thompson, Day, Boyd & Marsden, 1991*b*) that TMS excites corticospinal neurones either at the initial segment (Edgley, Eyre, Lemon & Miller, 1990) or at a presynaptic level via cortical afferents or interneurones (Amassian, Stewart, Quirk & Rosenthal, 1987; Day *et al.* 1989*a*; Amassian, Quirk & Stewart, 1990). Despite a recent note of caution regarding the assumption that responses to transcranial electrical stimulation are independent of cortical excitability (Hicks, Burke, Stephen, Woodforth & Crawford, 1992), there is general agreement that the cortical elements excited by TMS are not restricted to corticospinal axons (Rothwell *et al.* 1991*b*). The aim of the work presented here was to determine whether TMS excites neurones at a cortical level that have inhibitory

connections with corticospinal neurones and, if so, to reveal details of how those inhibitory inputs are organized.

When TMS is applied to the brain during voluntary activation of muscles, the compound motor-evoked potential (cMEP) may be followed by a period in which the EMG is suppressed or absent (Calancie, Nordin, Wallin & Hagbarth, 1987), often called a silent period. There are several mechanisms that could contribute to such suppression, including after-hyperpolarization of motoneurones, disfacilitation of motoneurones as a result of a reduction in supraspinal or segmental excitatory drive and activation of inhibitory inputs at the level of the spinal cord. H reflexes and electrical stimulation of corticospinal axons have been used to test the excitability of spinal motoneurones during the suppression of EMG in response to TMS. In several studies, a test response during the period of suppression was increased, or not reduced, relative to the response at rest, suggesting that part, at least, of the suppressed firing of motoneurones is due to a reduction in cortical output rather than inhibition of motoneurones (Day, Marsden, Rothwell, Thompson & Ugawa, 1989*b*; Rothwell, Day, Thompson & Marsden, 1989; Cros *et al.* 1991; Fuhr, Agostino & Hallett, 1991). The suppression following excitation to TMS has been reported as shorter than normal in Huntington's disease (Eisen, Bohlega, Block & Hayden, 1989), Parkinson's disease and hemiplegia (Haug, Schonle, Knobloch & Kohne, 1992). Since these disorders primarily affect structures in the brain rather than the spinal cord, these results again suggest that a component of the suppression of EMG in response to TMS may be due to inhibition of corticospinal output.

Suppression of voluntary contraction in response to TMS has been observed in the absence of preceding excitation in muscles ipsilateral to the stimulus (Wassermann, Fuhr, Cohen & Hallett, 1991*a*). In addition, low-intensity TMS caused a reduction in EMG of contralateral muscles, also in the absence of cMEPs (Wassermann, Pascual-Leone, Valls-Sole, Cohen & Hallett, 1991*b*). These authors stressed the importance of coil position and speculated as to whether the suppression had a cortical or spinal cord mechanism.

Single motor unit studies have identified short latency suppression of discharge to TMS in some units in normal man (Palmer & Ashby, 1992; Ellaway, Davey & Maskill, 1993), in multiple sclerosis (Boniface & Mills, 1992) and in motor neurone disease (Triggs *et al.* 1991), in the absence of any preceding excitation.

Responses to a magnetic test shock to the cortex can be inhibited when the test shock is preceded by an electrical or magnetic conditioning shock (Rothwell, Ferbert, Caramia, Kujirai, Day & Thompson, 1991*a*). Further work (Kujirai *et al.* 1991; Ferbert, Priori, Rothwell, Day, Colebatch & Marsden, 1992) demonstrated that responses to test shocks were inhibited by conditioning shocks applied to the opposite hemisphere, suggesting the presence of a transcallosal inhibitory pathway. These authors also reported an ipsilateral suppression of voluntary activity in response to TMS.

In this study we have examined suppression of voluntary muscle activity in the hand and arm in response to low-level TMS of the motor cortex in normal subjects. We have investigated the site at which TMS elicits suppression and the orientation at which the induced current is most effective. We also present evidence to suggest that the suppression caused by TMS during voluntary contraction is primarily a reduction in corticospinal output rather than an inhibition of motoneurones at the level of the spinal cord. Preliminary accounts of this work have been published (Davey, Romaiguère, Maskill & Ellaway, 1992, 1993*b*, *c*; Ellaway *et al.* 1993).

METHODS

A total of fifteen normal subjects (aged 23–63 years; 11 male, 4 female), none of whom had ever been referred to a neurologist, took part in these studies. Ethical approval was obtained from Charing Cross and Westminster Medical School and all subjects gave their informed consent to take part in the study.

Electrophysiological recording

Electromyograms (EMG) were recorded using self-adhesive surface electrodes (Arbo Neonatal Pink). All recordings were made, irrespective of handedness, from the right arm/hand. One electrode was placed on the skin overlying the muscle under study and another was placed over a neighbouring area of skin overlying bone. A metal plate was strapped to the right arm to act as an earth electrode. In several of the experimental protocols EMG recordings were made using electrodes placed over the thenar eminence of the hand. Using this recording arrangement much of the EMG signal originates from the adductor pollicis muscle. However, we cannot exclude contributions to the recording from flexor pollicis brevis, abductor pollicis brevis and the opponens pollicis muscle. In one section of the study, simultaneous EMG recordings were made from the second and third dorsal interosseus (2DI and 3DI) muscles of the hand. The close anatomical disposition of these two muscles results in electrical cross-talk when surface electrodes are used to record EMG. To avoid this problem, monopolar needle electrodes were inserted into each of the two muscles and EMG recordings were made against a common indifferent surface electrode placed over the metacarpo-phalangeal joint.

All EMG signals were filtered (−3 dB at 300 Hz and 10 kHz) and amplified (× 1000) before being sampled by a computer for analysis (Cambridge Electronic Design 1401/IBM-compatible PC) and recorded on a four-channel magnetic cassette tape deck (Tascam, Syncaset 234).

The subjects were provided with audio feedback of their EMG signals from a loudspeaker and a visual display from a cathode ray oscilloscope. This monitoring enabled the subjects to provide a constant and low level of EMG signal in the muscle throughout those parts of the study requiring a steady level of voluntary contraction.

Transcranial magnetic stimulation (TMS)

Electromagnetic stimulation of the brain was achieved using a 1·5 Tesla Magstim 200 (MagStim Company) stimulator. The stimulator was connected to either a 9 cm, average diameter, circular or to a 'double' 7 cm, average diameter, figure-of-eight stimulating coil. Cross-wires were taped to either side of the circular stimulating coil to assist in accurate placement over

the cranium. In order to elicit responses in muscles on the right side of the body, the circular coil was placed tangentially on the head with the initial current flow in the coil being in an anticlockwise direction when viewed from above (Day *et al.* 1990). The protocols for positioning the coils and the orientations used for the figure-of-eight coil are described in the relevant section of the results.

Signal averaging and estimation of threshold

Unrectified and full-wave rectified EMG signals were averaged with reference to trigger stimuli using a Cambridge Electronic Design signal averaging software routine (SIGAVG). The number of sweeps employed depended on the scale of the response being investigated. The threshold for both excitation and suppression was assessed by averaging 100 responses to the magnetic stimulus. If, after 100 stimuli, it was not possible to resolve a response at the latency expected from the application of suprathreshold stimuli, then we deemed the stimulus to be subthreshold.

Averages of the full-wave rectified EMG were used to assess the form and extent of responses to TMS. In addition, averages of unrectified traces have been examined routinely to ensure, for example, that a period of suppression was not preceded by a small facilitatory response in some trials. Such a weak and infrequent excitatory response within the variable on-going EMG of a voluntary contraction may not be rectified about its true zero reference level and may be missed or even be misinterpreted as inhibition (see Widmer & Lund, 1989).

Electrical stimulation of cervical spinal cord

Electrical stimulation of the cervical spinal cord was employed to produce responses in muscles of the right hand. A Digitimer (D180) stimulator attached to a pair of stimulating electrodes (D180/031) was used to stimulate the spinal cord in the cervical region. Responses in the hand muscles were evoked at 30–50 % of the maximum output of this stimulator using a pulse-width setting of 50 μs. The cathode stimulating electrode was placed on the skin between the C6 and C7 vertebrae. The anode was positioned a fixed distance (6·5 cm) away, usually over the C2 vertebra.

The following tests were carried out to ensure that the electrical stimulus was accessing presynaptic elements within the spinal cord rather than axons of motoneurones in peripheral nerve roots. First, the site of exit of the peripheral nerve roots for the thenar muscles (C7) was explored with the electrical stimulator. The direct response of the muscle, to just suprathreshold stimulation, invariably had a latency 1–2 ms shorter than the response to stimulation between C6 and C7 vertebrae. Extra conduction time for the response to stimulation at the C6/C7 site would have amounted to less than 0·5 ms of the 1–2 ms (assuming a motor axon conduction velocity of 60 m s^{-1}), making it unlikely that stimulation between C6 and C7 was accessing peripheral nerve roots. Second, the subject was asked to make a weak voluntary contraction (5–10 % maximum voluntary contraction). The mean amplitude of each of ten or twenty rectified and unrectified responses was assessed over a fixed time interval in both the relaxed and voluntarily activated state. The time interval was taken as the maximum duration of the response produced in either situation. In all cases, responses evoked during voluntary activation were significantly larger (Student's unpaired t test, $P < 0{\cdot}01$) than those produced while the muscle was relaxed. This again indicated that stimulation of the thenar muscles was unlikely to have been a result of the activation of peripheral motor axons. Stimulation at C6/7 may have activated any of a number of different structures, including descending spinal cord axons, primary afferent axons, interneurones or thenar motoneurones directly, although the last mentioned would be expected to have a high threshold (Ranck, 1975). Despite the fact that we cannot conclude that the stimulus preferentially excited the large axons of the corticospinal tract, stimulation of any of these structures provides a test of the excitability of the motoneurones at the spinal cord level.

In some subjects, electrical stimulation at C6/7 produced a small EMG response at a latency 1–2 ms shorter than the main component of the response. In these cases, it was the latter component only that could be facilitated by voluntary effort, suggesting that the early component was due to direct stimulation of motor axons. The presence of the early component did not invalidate the procedure, which was designed to test the excitability of motoneurones at the level of the spinal cord. The later response would have been contributed by motor units with axons that were not excited directly by the stimulus and thus were not refractory. Those motor units, and the units recruited during the voluntary effort, would have been excited by presynaptic elements responding to the spinal cord stimulus.

Conditioning magnetic stimulation of the brain was delivered in an attempt to modify test responses to the spinal cord stimuli. Conditioning TMS was applied prior to every other electrical stimulus to the spinal cord. The mean amplitude of each response was measured (as above) and the conditioned responses were compared with the test responses using Student's unpaired t test.

RESULTS

Suppression of voluntary muscle activity

A 9 cm circular stimulating coil was placed over the low-threshold site (see Methods) for producing excitatory responses in the right thenar muscles with the induced current flowing in a clockwise direction. The subject was asked to voluntarily activate the right thenar muscles to a level of about 5–10 % of maximum voluntary contraction (MVC). The records shown in Fig. 1 include averages of rectified (Fig. 1*A*) and non-rectified (Fig. 1*B*) EMG responses of the right thenar muscles to ten TMS at 45 % (percentage of maximum stimulator output) presented to the left hemisphere. Stimulation at time zero is evidenced by a stimulus artifact. The level of voluntary EMG activity can be seen in the time period a few milliseconds before and after the stimulus. In this subject, a cMEP was produced in response to TMS with a latency of 23 ms and a duration of approximately 15 ms. A period of reduced EMG activity followed the cMEP.

Figure 1 also shows averaged responses (Fig. 1*C* rectified, Fig. 1*D* unrectified) at enhanced gain and with a reduced stimulus strength, using the same subject and protocol. The recording was made a few minutes later in the experimental session with the stimulating coil and recording electrodes in the same position. The stimulating intensity (35 % maximum stimulator output) was subthreshold for excitation of the right thenar muscles, but produced a reduction in the

voluntary EMG at a latency of 27·5 ms (4·5 ms longer than the excitation evoked in Fig. 1*A* and *B*). The suppression evident in Fig. 1*C* represented a reduction in EMG of about 50 % (mean level of 15 μV reduced to 7·5 μV) from the prestimulus level and had a duration of approximately 15 ms in this record. The averaged record of the non-rectified traces in Fig. 1*D* showed no stimulus-locked components, confirming that the dip in the averaged rectified traces (Fig. 1*C*) was not preceded by a small excitatory potential.

A number of other hand and arm muscles were examined to see whether suppression of voluntary contraction with TMS at a strength below that which produced short-latency excitation was a general feature. Figure 2 illustrates instances of suppression of voluntary EMG activity in the absence of preceding excitation in response to TMS in seven separate hand and arm muscles. Suppression was observed in these muscles in the majority of subjects that were examined. Suppression was obtained in six out of six subjects (6/6) for the first dorsal interosseus (1DI), 6/11 for the second dorsal interosseus (2DI), 7/11 for the third dorsal interosseus (3DI), 3/4 for abductor pollicis longus (APL), 2/3 for wrist extensor and 3/4 wrist flexor muscles. Seven of the fourteen subjects were then selected because suppression to weak TMS had already been observed in one or more of these muscles. Suppression of voluntary EMG in thenar muscles was observed in all seven subjects. The duration and strength of the suppression presented in Fig. 2 appeared to vary between muscles. However, we have not studied the pattern of suppression in these different muscles systematically. Differences in stimulus strength, subject and muscle could all have contributed to the observed variability.

In a number of instances a period of increased EMG activity was observed following the suppression in response to TMS (Fig. 2). The presence of this late response was not systematically associated with a particular muscle or subject.

The latency of suppression of voluntary contraction in response to TMS, in the absence of excitation, was invariably longer than that of excitation elicited on increasing the stimulus strength. The mean latencies for excitation were 22·5 ± 1·7 ms (S.D.) for 2DI and 3DI and 23·5 ± 1·6 ms for thenar muscles, and for suppression were 26·2 ± 1·3 ms for 2DI and 3DI and 29·8 ± 1·6 ms for thenar muscles. Figure 3*A* illustrates the latency differences between the suppression of voluntary EMG by TMS and

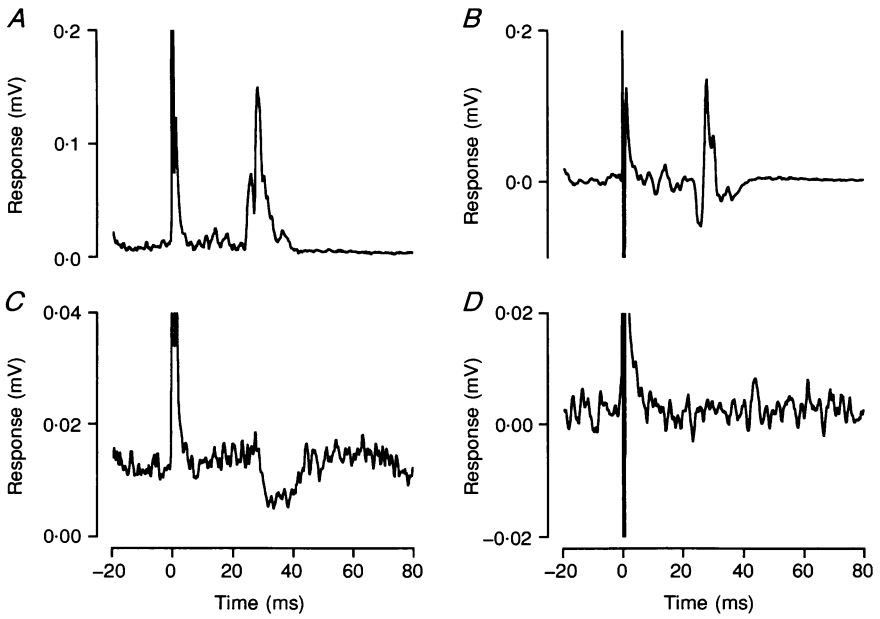

Figure 1. Responses of thenar muscles to TMS of the motor cortex during voluntary contraction
A and *B*, averages of rectified (*A*) and unrectified surface EMG (*B*) of right thenar muscles to 10 transcranial magnetic stimuli delivered to the left hemisphere at 45 % maximum stimulator output. A 9 cm circular coil was placed over the low-threshold site for excitation of the thenar muscles of the right hand. The subject was producing an isometric voluntary contraction at a level of 5–10 % maximum voluntary contraction. *C* and *D*, averages of rectified (*C*) and unrectified surface EMG (*D*) in the same subject under identical conditions to those in *A* and *B*, but using 50 transcranial magnetic stimuli at 35 % maximum stimulator output. No excitatory responses are evident in either the rectified (*C*) or unrectified averages (*D*). Suppression of voluntary activity is evident in the rectified, averaged response (*C*). The suppression has a latency 4 ms longer than the excitation in *A* and *B*. The suppression has a duration of 15 ms and represents approximately a 50 % decrease in the background EMG level. Stimulus artifacts at time zero in the EMG records mark the time of stimulation. Note dissimilar gains in *A* and *B* compared with *C* and *D*.

the excitatory responses observed at higher stimulus intensities for 2DI, 3DI and the thenar muscles of the hand. In the seventeen examples, suppression had a latency ranging from 3 to 8 ms longer than excitation. Figure 3*A* suggests a bimodal distribution of latency differences, albeit with some overlap, having modal values of 3·5 and 7·5 ms for the DI and thenar muscles respectively. Several limitations, including lack of precision in measuring the exact time of onset of suppression and non-standardization of stimulus strengths between subjects, makes any interpretation of this bimodality premature.

Figure 3*B* shows that the duration of the suppression evoked by TMS ranged from 7·5 to 27·5 ms with fourteen instances out of seventeen falling in the range 7·5–12·5 ms. It has not been possible to examine systematically the effect of stimulus strength on depth and duration of the suppression. In general, an increase of less than 5 % of the maximum output of the stimulator, above the stimulus strength that was threshold for suppression of EMG activity, was sufficient to produce an early excitatory response. At such stimulus strengths the excitation, having a shorter latency but a duration that exceeded the expected latency of the suppression, obviously obscured the initial component of that suppression.

Location and orientation of magnetic stimulus

Two studies were conducted to determine the position and orientation of the stimulating coil at which excitatory and inhibitory responses had the lowest threshold to magnetic stimulation.

The design of the first experiment is illustrated in Fig. 4. In six subjects (aged 28–49 years) a 9 cm circular stimulating coil was used with the induced current flowing clockwise. EMG was recorded with surface electrodes from the thenar muscles of the right hand. The coil was centred on each of five points, placed 2 cm apart, lying on a transverse line 2 cm posterior to the vertex (Cz). The line extended from a point 6 cm to the left of Cz to a point 2 cm to the right of Cz. In our experience, hand muscle responses can be elicited at lowest stimulus strength with a 9 cm circular stimulating coil centred close to the point 2 cm to the left of Cz on this line. Subjects were asked to produce a low level of voluntary activity (5–10 % MVC) in the thenar muscles and to relax other hand and arm muscles. At each point on the line, a

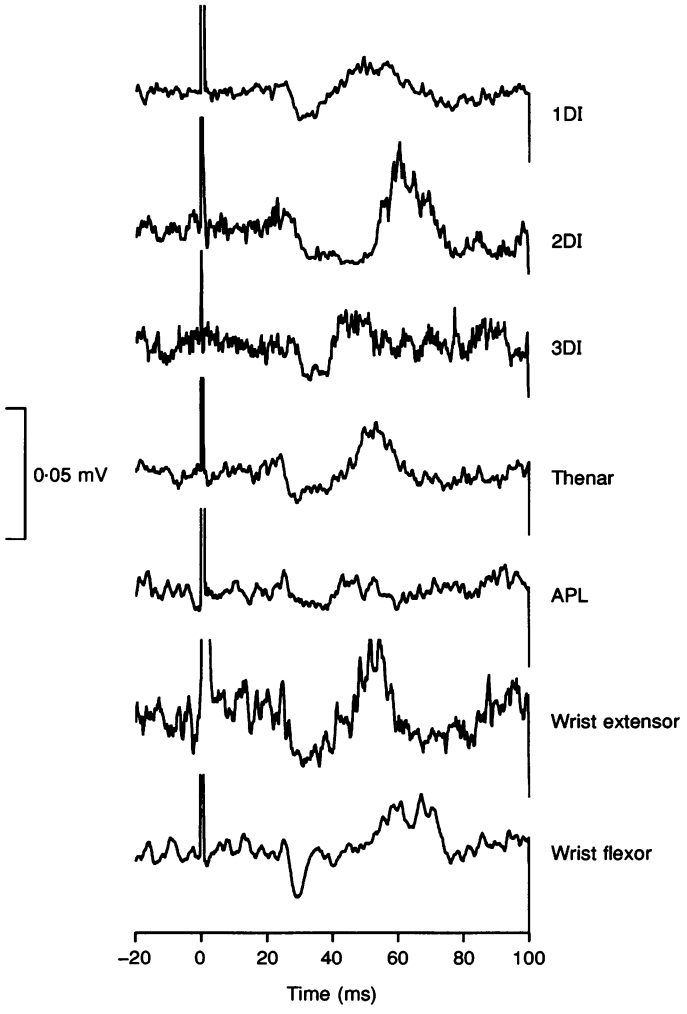

Figure 2. Suppression of voluntary EMG in different muscles of the arm and hand evoked by TMS

The figure represents recordings made in several subjects. For each recording, a 9 cm circular coil was placed over the low-threshold site for producing excitatory responses in that muscle. Responses are rectified and averaged ($n = 30$–80). Stimulation occurred at time zero and results in a stimulus artifact in each record. In each case, the strength of the TMS was a few per cent of maximum stimulator output below that which would have produced a clearly identifiable excitatory response at a latency shorter than the suppression seen in the records. The bottom of the vertical line at the end of each record marks the zero level of EMG. Abbreviations: 1DI, 2DI, 3DI, first, second and third dorsal interossei; APL, abductor pollicis longus.

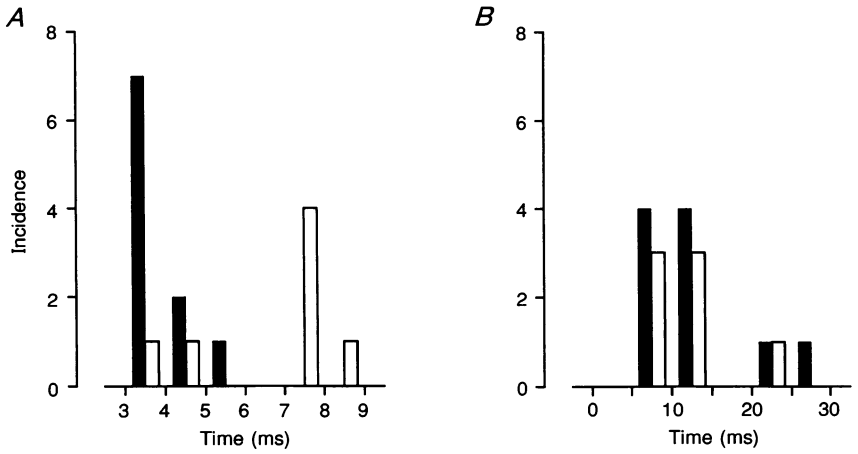

Figure 3. Latency and duration of suppression of voluntary contraction produced by TMS of the motor cortex

A, latency differences between suppression observed in the absence of preceding excitation and excitatory responses seen at higher stimulation strength. *B*, duration of suppression of voluntary activity evoked by TMS in the absence of preceding excitation. The data are derived from 3 hand muscles (■, 2DI and 3DI; □, thenar muscles) in 9 different individuals.

number of different stimulus strengths, differing by 2 % of maximum stimulator output, were employed to assess the thresholds for excitatory and inhibitory responses.

Figure 4 shows the threshold stimulus strengths (percentage of maximum stimulator output) for suppression (○) and excitation (●) for the five stimulation sites. In five of the six subjects, the threshold for suppression was lower than that for excitation at all points. In one subject (Fig. 4, Subject 5), it was possible to evoke suppression in the absence of excitation only at two of the five locations tested. Excluding that subject, the lowest threshold coil position for excitatory responses coincided with the lowest threshold site for suppression of voluntary activity. In general, the centre of the coil in this position lay between

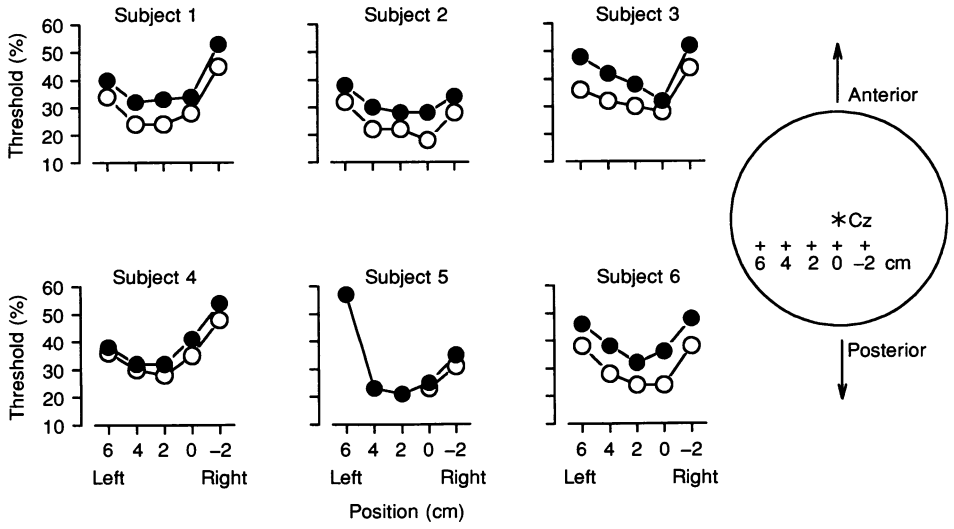

Figure 4. Location of low-threshold sites for excitation and suppression of contraction in response to TMS of the motor cortex

Thresholds (% maximum stimulator output) for excitatory responses (●) and suppression of voluntary contraction (○) plotted against position of the centre of a 9 cm circular stimulating coil. Data are from the right thenar muscles during voluntary contraction in 6 subjects. The diagram to the right represents the top of the head with the coil positions marked at 2 cm intervals on a transverse line 2 cm posterior to the vertex (Cz). Note that, with the exception of Subject 5, suppression is invariably evoked at a lower stimulation intensity than excitation at all coil positions.

the vertex and a point 2 cm to the left. The findings illustrated in Fig. 4 suggest that the structures within the cortex responsible for producing the observed suppression lie in close proximity to those that produce excitation.

The second study set out to establish how the orientation of the induced current for eliciting suppression of voluntary activity compared with that for eliciting excitation. The design of the experiment is shown in Fig. 5. Four subjects (aged 28–49 years; same as Subjects 1–4 above) took part in the study, in which we used a 7 cm figure-of-eight stimulating coil. The initial current in the wiring of the coils at the cross-over of the figure-of-eight flows towards the handle (manufacturer's specification). On the first trial, the coil was held over the left side of the head with the handle towards the posterior aspect along a sagittal line. In that orientation of the coil, the strongest induced current in the brain travelled in a posterior-to-anterior direction. The low-threshold site for producing excitation in the right thenar muscles was determined and the centre of the figure-of-eight coil retained at this location. This point was located 1–2·5 cm anterior and 2–4·5 cm lateral (left side) to the vertex for the four subjects. The location coincided with the position occupied by part of the winding of the circular coil when it was positioned over the low-threshold location for excitation of thenar muscles. As in the previous study, thresholds for both excitation and suppression were assessed during voluntary contraction. The coil was then rotated in 45 deg steps through 360 deg and thresholds for both excitation and suppression were assessed at each step, i.e. with eight different vectors of induced stimulating current.

In Fig. 5, the centre of each 'spider' diagram represents the position of the cross-over point of the figure-of-eight stimulating coil. The direction of the lines away from the centre represents the direction of the induced stimulating current. The length of line (see scale bar) is directly proportional to the threshold (percentage of maximum stimulator output) for an excitatory response (thin lines) or suppression of voluntary activity (thick lines). In all subjects, excitation had a higher threshold than suppression at all eight orientations of the coil, with one exception (orientation anterior and to the right in Subject 1). In all

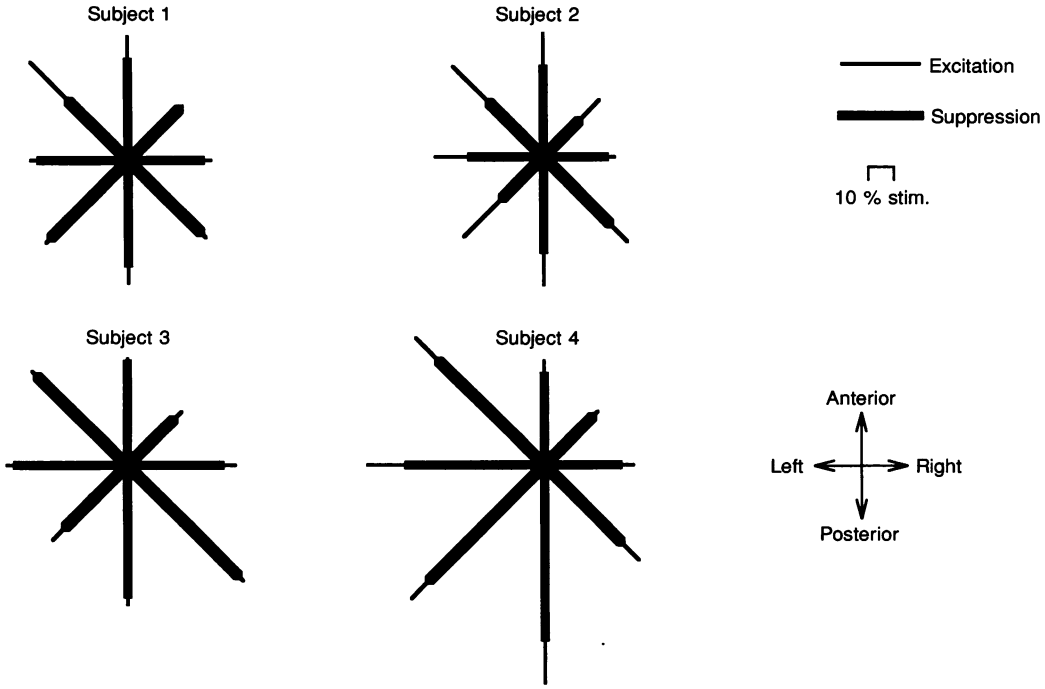

Figure 5. Strength of TMS required to produce threshold excitation and suppression of voluntary activity in thenar muscles at different orientations of a figure-of-eight stimulating coil in four subjects

The length of the 8 lines in each spider diagram (see scale bar) indicates thresholds (% maximum stimulator output) for excitation (thin lines) and suppression (thick lines) at different orientations of induced stimulating current flowing away from the centre. The cross-over point of the figure-of-eight was placed over the low-threshold site for excitation of the right thenar muscles. This location was found to lie over the left side of the cranium approximately 2–4·5 cm to the left and 1–2·5 cm anterior to the vertex. Suppression had a lower threshold than excitation in all subjects and at all orientations with the exception of one orientation in subject 1. The lowest thresholds for both responses in all subjects were found with the induced current flowing antero-medially (i.e. anterior and to the right). Subjects 1–4 are the same as those numbered 1–4 in Fig. 4.

subjects, the lowest threshold orientation for both excitatory and inhibitory responses was with the induced current flowing anterior and to the right (antero-medially).

Investigation of the site of the inhibitory mechanism

Absence of coincident excitation in response to TMS in another muscle

One possible cause of the suppression of EMG activity during a voluntary contraction could arise if there was simultaneous excitation by TMS of motoneurones to other muscles. A corticospinal volley would activate interneurones at the level of the motoneurones in the spinal cord. Ia inhibitory interneurones mediating reciprocal inhibition are excited by corticospinal neurones (Jankowska, Padel & Tanaka, 1976) and the discharge of motoneurones could excite recurrent inhibitory interneurones. If the suppression of voluntary activity that we observed in response to TMS was a result of a corticospinal volley activating spinal inhibitory interneurones, then the observed suppression of EMG in one muscle should have been accompanied by facilitation or excitation of other muscles.

The protocol for this investigation required the simultaneous voluntary activation of two muscles, preferably those having an antagonist action. The voluntary effort produced on-going discharges of motoneurones to both muscles under study, which obviated consideration of the possibility of subthreshold corticospinal facilitation of one muscle during suppression of EMG in the other. It was also necessary to be able to elicit responses in both muscles with TMS applied to the same site on the head. In practice, the requirements for this protocol limited the choice of muscles. We studied 2nd and 3rd dorsal interrossei (2DI and 3DI) muscles, which are intrinsic to the hand. These muscles are antagonistic in that they cause abduction of the middle finger in different directions, although they may be activated as physiological synergists in some tasks. Eleven subjects (aged 23–63 years) took part in this study. They were asked to co-contract 2DI and 3DI muscles approximately equally and, after practice, were able to achieve this using auditory feedback of EMG signals. Because of the close proximity of the two muscles, EMG recordings were made using monopolar needle electrodes to avoid cross-talk through the skin. A 9 cm circular stimulating coil was positioned so as to evoke excitatory responses of approximately equal magnitude in the two muscles. The stimulus strength was then reduced until no excitatory responses were seen in either muscle. The records in Fig. 6 show averages of 100 rectified responses in 2DI and 3DI with TMS delivered at 33 % (percentage of maximum stimulator output). These records show pronounced suppression in both muscles with a latency of 26·5 ms and duration of approximately 22 ms. There is no evidence of prior excitatory responses in either muscle. In seven of the eleven subjects, suppression was seen in one ($n = 1$) or both ($n = 6$) muscles in the absence of prior excitation in either.

Response to spinal cord stimulation conditioned by TMS

In a second experimental procedure, the excitability of motoneurones of the right thenar muscles was tested by stimulation designed to excite descending tracts at the level of the cervical spinal cord (see Methods). An electrical stimulus was applied through electrodes placed over the C2 (anode) and C6/7 (cathode) vertebrae. We confirmed that the stimulus was exciting structures within the spinal cord by ascertaining that the responses had a latency 1–2 ms longer than those excited by deliberate placement of the cathode at the point of emergence (C7) of the spinal roots for the thenar muscles (Mills & Murray, 1986). Also, in

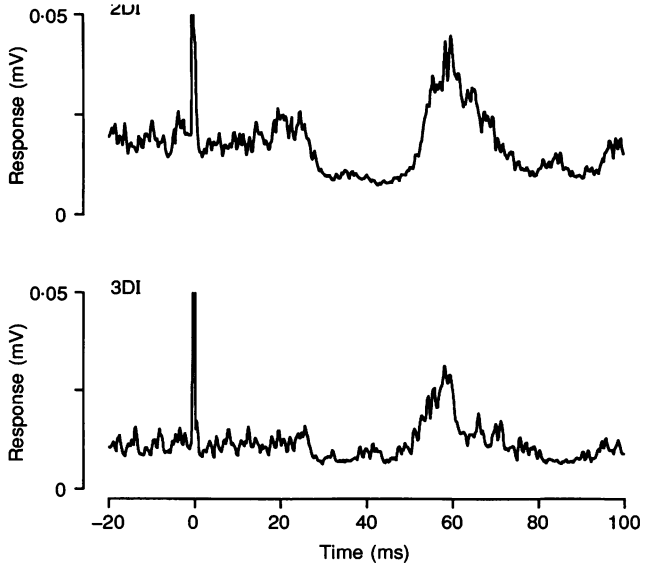

Figure 6. Concurrent suppression of voluntary contraction in antagonist muscles evoked by TMS
The simultaneous recordings are from 2DI and 3DI and were constructed from averages of 100 rectified responses to TMS delivered at 33 % (% maximum stimulator output). TMS was delivered with a 9 cm circular coil centred over the optimal site for equal excitation of both muscles when tested at higher stimulus strength. TMS occurs at time zero and produces an artifact in each record. The EMG recordings were made with monopolar needle electrodes inserted into each muscle. NB averages of the unrectified traces showed no stimulus-locked excitatory responses prior to the suppression of EMG.

every instance we confirmed that the responses could be facilitated by voluntary activation of the muscle. This check is illustrated in the inset of Fig. 7 and is discussed more fully in the Methods.

It is noticeable that the late component of the response to electrical stimulation of the spinal cord showed the most facilitation. It is possible, therefore, that part of the earliest component of the response to electrical stimulation could be a consequence of direct excitation of motoneurone axons. Alternatively, the potentials could have resulted from fast conducting motoneurone axons of large anterior horn cells that were activated presynaptically by the electrical stimulus but not by the corticospinal activity resulting from the weak voluntary effort. Whichever was the case, their presence does not preclude the response to electrical stimulation of the cord being due, at least in part, to activation of motoneurones in the spinal cord and not solely of axons of motoneurones in the spinal roots or peripheral nerve.

Electrical stimulation of the spinal cord was used to produce 'test' responses in the right thenar muscles which we attempted to condition by prior magnetic stimulation of the motor cortex. The strength of the conditioning magnetic stimulation used was at a level that produced suppression of voluntary activity in the right thenar muscles in the absence of any excitatory response (see Fig. 7*A*). The interval between the conditioning and test stimuli was set so that the excitatory response to the test (spinal cord) stimulus fell during the expected period of suppression resulting from the conditioning stimulus. Conditioning–test intervals in the range 13–16 ms were used.

If weak TMS excited a corticospinal volley that inhibited motoneurones in the spinal cord, then the test response to spinal cord stimulation would be inhibited by prior conditioning TMS in both the relaxed state and during the facilitation caused by voluntary activation. In contrast, if weak TMS reduced the activity in the corticospinal neurones, then it might reduce the response to spinal cord stimulation by a process of disfacilitation of motoneurones during voluntary contraction, but would not reduce the response in the absence of voluntary activation. The following experiments were carried out to distinguish these possible modes of action. Experiments were carried out on subjects with both relaxed and voluntarily activated thenar muscles.

Figure 7*B* shows the averaged response in the thenar muscles to an electrical stimulus to the spinal cord during voluntary contraction. The stimulus intensity was set to produce a weak (approximately 10 % maximum) response in the muscle in order that any weak inhibition elicited by conditioning TMS would not be obscured by a strong excitatory drive. The averaged response to the same test electrical stimulus was reduced slightly in magnitude (Fig. 7*D*) by prior conditioning with TMS at 36 % of maximum output, a strength sufficient to cause suppression of EMG activity during voluntary contraction in the absence

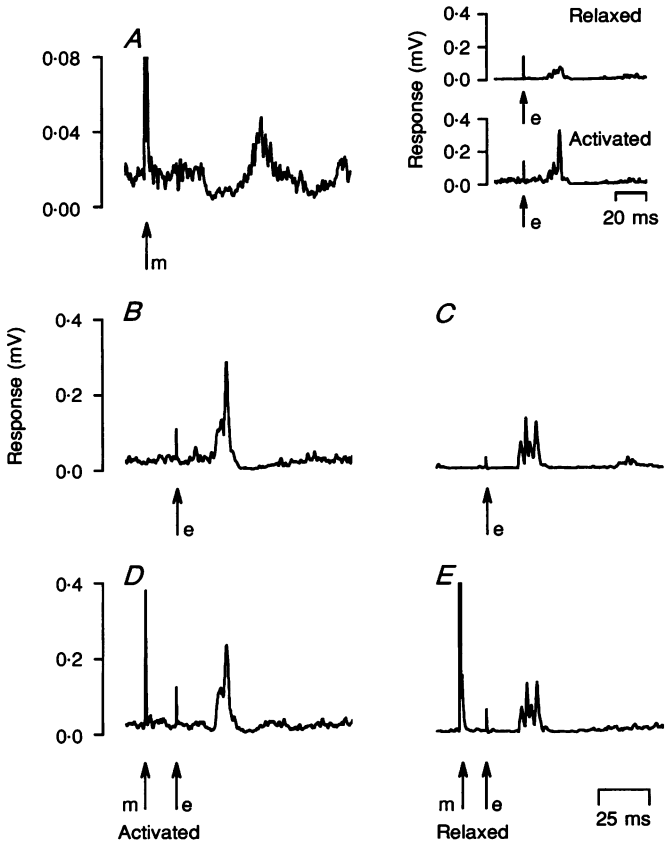

Figure 7. TMS conditioning of the EMG responses in the right thenar muscles to test electrical shocks to the spinal cord in a single subject
Inset, averages of 10 rectified responses to test electrical stimulation of the spinal cord in the relaxed muscle (top) and during voluntary activation (bottom). *A–E*, averages of twenty rectified responses. *A*, suppression of voluntary activity to TMS delivered at 36 % (% maximum stimulator output). Suppression occurred with a latency of 28 ms and had a duration of 24 ms. *B*, excitation in response to electrical stimulation of the spinal cord in the cervical region during voluntary activation. *C*, protocol as in *B*, but with the muscles relaxed. *D*, response to electrical stimulation of the spinal cord in the cervical region conditioned by prior TMS during voluntary activation. Strength of TMS was the same as in *A*. *E*, protocol as in *D*, but with the muscle relaxed. Test electrical stimuli are indicated by the arrows marked 'e' and conditioning TMS by the arrows marked 'm'.

of prior excitation. However, when pairs of conditioned and non-conditioned test responses were compared in this subject, the reduction was not found to be statistically significant (Student's unpaired t test, $P > 0{\cdot}01$). Conditioning with TMS failed to produce any change in a test response to spinal cord stimulation during voluntary contraction in eleven of thirteen trials in four subjects. Small, but significant ($P < 0{\cdot}01$) reductions were produced in only two trials.

Figure 7*C* and *E* shows responses in the relaxed thenar muscles, in the same subject, to test spinal cord stimuli of the same magnitude used in the activated muscle (Fig. 7*B* and *D*). Under these conditions, prior conditioning TMS, at a strength that produced suppresssion of voluntary EMG, failed to influence the test response (Fig. 7*E*). In none of five trials (3 subjects) in the relaxed state was the test response conditioned by TMS significantly different from the response to the spinal cord test shock alone. We interpret this as indicating that the cortical conditioning TMS was not exciting a descending volley that caused inhibition of motoneurones at the level of the spinal cord.

DISCUSSION

The results of this study firmly establish that TMS of the contralateral motor cortex in normal man can elicit suppression of voluntary contraction in the absence of preceding excitation (Wasserman *et al.* 1991*b*; Cantello, Gianelli, Civardi & Mutani, 1992; Davey *et al.* 1992; Palmer & Ashby, 1992; Davey *et al.* 1993*b*,*c*; Ellaway *et al.* 1993). It is clear, therefore, that such suppression is not restricted to disease states in which the threshold for excitatory responses to TMS may be raised (Triggs *et al.* 1991).

Preferred coil location and orientation

Previous work (Mills, Boniface & Schubert, 1992) has indicated that the size of the motor-evoked potential response produced by TMS of the motor cortex depends on the direction of the induced stimulating current. We found this also to be the case when determining threshold levels for eliciting suppression of voluntary EMG by TMS. In each of the four subjects investigated with a figure-of-eight coil, the orientation of induced current with lowest threshold for excitatory responses was found to be the same as that for eliciting suppression of voluntary activity. This orientation was such that the induced stimulating current travelled in an antero-medial direction at the site of stimulation over the left hemisphere. The site of stimulation under the centre of the figure-of-eight coil corresponded with a point on the perimeter of the circular coil when that coil was positioned at its low-threshold site for excitation of the thenar muscles. In addition, the tangent to the rim of the circular coil, and presumably the direction of the underlying induced current, also had a general antero-medial orientation at that location. It is likely, therefore, that the cortical neurones responsible for both excitatory responses and suppression of voluntary activity were activated by both coils at the same location with reference to a point on the surface of the scalp. Furthermore, our results suggest that the underlying cortical structures being stimulated during suppression and excitation not only have shared locations with reference to location of the coil on the surface of the head, but also that the neuronal elements involved have similar orientations. The significance of this finding will remain unclear until a more accurate picture emerges of the structures within the cortex that are excited by TMS (Maccabee, Amassian, Eberle & Cracco, 1993). Also, it should be borne in mind that the resolution in this experiment was only 45 deg and smaller differences in orientation of the structures producing suppression and excitation would not have been detected.

Spinal *versus* cortical mechanism?

It might be argued from our findings that suppression of voluntary EMG and excitation could be evoked by TMS at a similar location on the head, and with the same orientation of induced current, that both responses result from excitation of corticospinal neurones. Although TMS is undoubtedly accessing the cortex, the mechanism responsible for the reduction in voluntary muscle activity could have been inhibitory interneurones located at the motoneuronal level in the spinal cord. Candidates for such an action are the disynaptic corticospinal activation of group Ia inhibitory interneurones (Jankowska *et al.* 1976) or recurrent inhibition. Ia inhibitory interneurones may be activated by collaterals of corticospinal axons to motoneurones of a muscle undergoing excitatory drive. A corticospinal volley that excites a muscle may indeed inhibit motoneurones of an antagonist muscle (Cheney, Fetz & Palmer, 1985). Two muscles that have antagonistic actions in the hand were examined (second and third dorsal interosseus). These muscles were co-contracted with equal levels of voluntary drive and, as far as possible, with other muscles in the hand relaxed. When TMS was applied to the cortex, both muscles showed suppression in the absence of preceding cMEPs. Thus, TMS-evoked excitation to one of these muscles was not a prerequisite for the inhibition in the other. Insufficient is known about the complement of Ia inhibitory interneurone pathways (Day, Marsden, Obeso & Rothwell, 1984; Berardelli, Day, Marsden & Rothwell, 1987; Katz, Penicaud & Rossi, 1991) or the recurrent inhibitory loop (Creange, Katz, Meunier, Penicaud & Pierrot-Deseilligny, 1992; Rossi & Mazzochio, 1992) regulating motoneurone discharge to muscles of the human arm and hand to generalize from this result. In the case of human interossei muscles, reciprocal Ia inhibition and recurrent inhibition (Datta & Stephens, 1979) have been neither established nor discounted, although animal studies show that recurrent inhibition at least is less well developed in distal muscles of the cat forelimb (Illert & Weitelmann, 1989). Although we cannot exclude the possibility of subthreshold corticospinal depolarization of motoneurones

innervating other muscles, no twitch contractions were observed in response to TMS in either the dorsal interosseus or other muscles of the hand or arm. This result, therefore, does not support the notion that the suppression observed in the absence of prior excitation is due to corticospinal activation of spinal inhibitory interneurones.

Further experiments were conducted to investigate whether TMS-evoked suppression of voluntary activity has a cortical component that reduces corticospinal output or whether the stimulus excites a descending corticospinal volley that inhibits motoneurones at the spinal cord level. The spinal cord was stimulated electrically at the neck to produce test responses in the thenar muscles. The test shock most probably stimulated the spinal cord at a site presynaptic to motoneurones, or possibly motoneurone cell bodies, rather than peripheral α-motoneurone axons. This was evidenced by the fact that the response could be facilitated by voluntary activation of the muscle. This result, in itself, provides support for the recent findings by Maertens de Noordhout, Pepin, Gerard & Delwaide (1992) and Davey, Murphy, Maskill, Guz & Ellaway (1993*a*) that facilitation of corticospinal activation of motoneurones by voluntary effort in man can occur at the level of the spinal cord. Returning to the question of inhibition, conditioning TMS at an intensity shown to produce suppression of voluntary activity in the thenar muscles was applied prior to the test shock to the spinal cord. When the experiment was conducted with the muscle at rest, the test responses were unaffected by the prior conditioning TMS. The electrical stimulus had been adjusted to produce a weak test response in the muscle (approximately 10 % maximum) to ensure that any weak inhibitory action was not obscured by a strong excitatory drive. The absence of any effect suggests that the conditioning TMS was not producing inhibition of motoneurones via corticospinal activation of inhibitory interneurones at the level of the spinal cord. In the voluntarily activated muscle, the conditioning TMS also failed to reduce significantly the size of the test responses in most (11 out of 13) trials. In the two instances where a small, significant reduction was observed, the conditioning TMS may have elicited a corticospinal volley that inhibited motoneurones via interneurones at the level of the spinal cord. However, the reduction in the test response could equally be explained by an intracortical action that reduced cortical output. The reduction in excitatory drive in the corticospinal tracts would thus disfacilitate the motoneurones in the spinal cord and result in a smaller test response to the spinal cord stimulus.

Putative cortical mechanisms

The suppression of voluntary activity seen in this study had a latency 3–8 ms longer than excitation seen at higher intensity TMS. If we are correct in deducing that TMS inhibits corticospinal neurones, this latency difference implies that TMS excites neurones that mediate inhibition via a longer pathway than that involved in the excitation of corticospinal neurones. However, our mapping experiments revealed the loci for excitation and inhibition of thenar muscles to be the same, at least within the resolution of the test sites, which were located 2 cm apart. One source of intracortical inhibition could thus be the excitation by TMS of corticofugal neurones in the same part of the motor cortex which, via axon collaterals, excite inhibitory neurones that act on the corticospinal neurones maintaining the voluntary drive to the muscle under study. Indeed, it could be argued that excitatory corticospinal neurones to motoneurones of the muscle under study are excited at the same time, but that the numbers are small compared with the number of corticofugal neurones that inhibit those same corticospinal neurones. This might account for the suppression of voluntary activity in the absence of a direct motor-evoked potential. However, the corticofugal neurones are unlikely to be corticospinal, since suppression of voluntary activity is not accompanied by excitation of the same or other muscles. We also have to account for the longer latency of the suppression. The longer latency of the suppression could simply be due to slower conduction in the axon collaterals and the axons of small inhibitory neurones, coupled with synaptic delays. In addition, it is possible that the corticospinal neurones active during voluntary contraction, and inhibited by TMS, have slower axon conduction velocities than those excited by TMS at higher stimulus intensity. The suppression of corticospinal output would therefore appear as a reduction in peripheral EMG at longer latency than that recorded for excitation. Whatever the mechanism, it is unlikely that the inhibitory process could act quickly enough to suppress a concomitant response to TMS of the corticospinal neurones innervating the muscle under study.

The pathway involved in inhibition of cortical output by TMS could involve a longer route, such as the known inhibitory loop via the thalamus. In the cat, stimulation of superficial cortical neurones inhibits neurones of the ventrobasal thalamus (Andersen, Eccles & Sears, 1964), which would disfacilitate cortical pyramidal cells. In addition, the inhibition of thalamic cells is followed by rebound excitation, which could account for the increased EMG observed in our experiments at the end of some periods of suppression of voluntary EMG activity.

As argued above, the neurones activated by TMS may not share the same location in terms of depth within the cortex, since suppression of voluntary activity was consistently achieved with a lower stimulus strength than was necessary for excitation. Magnetic field strength falls off rapidly with distance away from the stimulating coil (Jalinous, 1992). The fact that the suppression of voluntary muscle activity is evoked in response to TMS at a lower strength than that required to produce excitation therefore raises the possibility that the structures excited by TMS and responsible for the suppression might lie in closer proximity to the stimulating coil. Jones (1975) reported that inhibitory GABAergic neurones are located throughout the

primate motor cortex, but they predominate in the most superficial layers I and II. The more superficial inhibitory neurones, despite their smaller dimensions (Jones, 1975), might therefore be activated preferentially by TMS of lower stimulus strength as a consequence of the shorter distance between their processes and the stimulating coil. However, such inhibitory neurones would have to be more superficial than the small pyramidal cells, which are difficult to excite with TMS (Edgley, Eyre, Lemon & Miller, 1992) or have an orientation of the excitable part of their processes that is more susceptible to currents generated by the magnetic field (Maccabee *et al.* 1993). Thus, although we find that excitatory responses and the suppression of voluntary activity to TMS share the same low-threshold site on the head, the relatively higher threshold for excitation may simply indicate that the neurones generating excitation lie deeper within the cerebral cortex.

Relevance to normal and abnormal movements

The inhibitory neurones activated by TMS are likely to be of relevance to normal movement, since it is known that a single stimulus can delay the initiation of voluntary movement (Day *et al.* 1989*c*; Rothwell *et al.* 1989). T hese workers suggested that the stimulus was inhibiting a group of strategically placed cortical neurones, so making them unresponsive for a brief period. The demonstration of inhibition of corticospinal output in normal man also raises the question of the status of cortical inhibition in central nervous system disorders. Of current interest is the finding that the excitability of the cortex is increased in epilepsy (Reutens & Berkovic, 1992; Fong *et al.* 1992). The present findings make it relevant to re-examine the situation using low-intensity TMS to find out whether this may in part be due to depression of intracortical inhibitory circuits.

In conclusion, we propose that inhibitory elements within the cortex can be activated by TMS. The location and orientation of the neuronal structures effecting suppression of voluntary EMG activity are similar to those involved in excitation of the same muscles. However, since suppression may be elicited at a lower stimulus strength, we suggest that the inhibitory circuitry may lie in more superficial layers of the motor cortex.

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