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Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements

A study using transcranial magnetic stimulation

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Summary

It is known that damage to the left hemisphere can lead to movement deficits, and that patients with apraxia have difficulty in selecting movements. Neurophysiological recording studies and lesion studies have shown that the premotor cortex is important for the selection of movements in monkeys. In this study we used transcranial magnetic stimulation (TMS) to disrupt the processing in human premotor cortex. We applied TMS to normal healthy volunteers over the premotor and primary motor areas while they carried out choice reaction time and simple reaction-time tasks. We measured response times of either hand as subjects were stimulated over the left and right hemisphere separately. We found that we were able to delay responses by stimulating at short cue–stimulus intervals (100–140 ms) over premotor cortex and at longer cue–stimulus intervals (300–340 ms) over primary motor cortex while subjects performed the choice reaction-time task with the contralateral hand. We were also able to delay responses with the ipsilateral hand while stimulating over the left premotor cortex, but not while stimulating over the right premotor cortex or either sensorimotor cortex. Premotor cortex stimulation alone disrupts an early stage of movement selection; motor cortex stimulation disrupts the movements at a later stage of execution. There was no distinguishing short cue–stimulus interval effect when premotor cortex was stimulated in the simple reaction time paradigm, where the movement selection demands of the task are kept to a minimum. We conclude that the premotor cortex is important for selecting movements after a visual cue and that the left hemisphere is dominant for the rapid selection of action.

Keywords: apraxia; premotor cortex; transcranial magnetic stimulation; motor learning; hemispheric lateralization

Abbreviations: ANOVA = analysis of variance; MEP = motor evoked potential; P (site) = premotor cortex (stimulating site); SM = sensorimotor cortex (stimulating site); TMS = transcranial magnetic stimulation

Introduction

It has been suggested that the dominant hemisphere for speech is also specialized for the selection of action (Kimura and Archibald, 1974; Kimura, 1993). Comparisons of patients with left and right hemisphere damage have found that patients who have damage to their left hemisphere with accompanying apraxia are bad at performing and copying sequences of movements, but not at copying single postures (Kimura and Archibald, 1974; Harrington and Haaland, 1992; Kimura, 1993).

The movements could be disrupted for several reasons. There could be impairments in kinematics and joint co-ordination (Poizner *et al*., 1990; Clarke *et al*., 1994; Poizner *et al*., 1995), impairments in the ability to plan sequences of movements (Poeck, 1982, 1985, 1986; Haaland and Harrington, 1992), or a failure in knowledge about the use of objects (De Renzi *et al*., 1980; De Renzi and Lucchelli, 1988). However, Rushworth *et al*. (1998) have argued that at least some patients are unable to select even single actions. They tested subjects on a conditional motor task in which one of four different joystick movements was selected depending on which colour patch cue was presented. Compared with right hemisphere patient control subjects, left hemisphere apraxics were slow to learn movement selection. The fact that the cues were plain colour patches and the

responses made with a joystick suggested that this deficit could not be explained by a kinematic impairment or an agnosic failure of knowledge about the use of objects.

The paradigm used in the experiment of Rushworth *et al*. (1998) is similar to a paradigm used in monkey experiments. The monkeys were taught a visual conditional motor task in which they were required to select between two different movements on the basis of visual cues. Halsband and Passingham (1982, 1985) taught monkeys to perform this task, and then removed the premotor cortex bilaterally (area 6); the animals were very impaired at relearning the task postoperatively. Petrides (1982) taught monkeys a similar task, and reported that after removal of premotor cortex (areas 6 and 8) the monkeys were unable to relearn the task. Further experiments have shown that this is not because the monkeys are unable see the cue or use the information provided by them (Petrides, 1986).

Rather than making permanent lesions, Kurata and Hoffman (1994) interfered temporarily with the activity of the dorsal premotor cortex by injecting muscimol. During the 10-min periods following the infusion, there was an increase in the number of errors made on a visual conditional motor task. The errors were errors of direction selection, not errors of movement execution.

Patients with dorsal premotor lesions have also been shown to be impaired in learning to select different movements on the basis of visual cues (Halsband and Freund, 1990). The patients were able to execute each of six movements used in the test and were able to distinguish each of six colour cues. However, they were unable to learn which movement was associated with each visual cue.

Apraxia has been thought to result from parietal lesions. However, Kertesz and Ferro (1984) have emphasized that there is usually damage to the deep white matter fascicles. Such lesions would disrupt fibres running from parietal cortex to the premotor and prefrontal areas. In most of the patients in the study by Rushworth *et al*. (1998) there were also disruptions of white matter, either under the parietal cortex or in the deep white matter fascicles running in the vicinity of the basal ganglia. These lesions may disrupt inputs to the premotor cortex.

Patients with apraxia tend to have large middle cerebral artery infarcts, so it is difficult to localize the critical regions. Many of the patients also have hemiparesis, and it is therefore only possible to measure the performance of the ipsilesional hand. Transcranial magnetic stimulation (TMS) has the advantage that it is possible to interfere with localized regions such as the premotor cortex. With TMS it is also possible to study the effect of interference at different times during the performance of a task. The stimulation pulse is very brief, ~600 μs, and the effect that it has on cortex lasts several tens of milliseconds. Stimulation over motor cortex can, for example, lead to delays of the onset of movements for up to 150 ms (Day *et al*., 1989). The temporal specificity allows one to investigate the time course of the recruitment of neurons in different areas of the brain.

The spatial specificity of TMS can be enhanced by using a figure-of-eight coil. This allowed us, not only to test each hemisphere independently, but also to distinguish between the effect of interfering with the activity of motor and premotor cortex. The estimated limit of spatial resolution for TMS maps using multiple averaged trials is ~5 mm (Brasil-Neto *et al*., 1992). We first located the hand representation for the primary motor cortex. The location of the dorsal premotor cortex was first estimated on the basis of the maps of premotor cortex derived from the PET studies of Fink *et al*. (1997). We then searched for the location at which there was maximal interference.

We studied the effects of stimulation on response times on simple and choice reaction-time tasks. In Experiment 1, we stimulated over both premotor and motor areas. We stimulated each hemisphere, and measured the effect of stimulation at different intervals on response times of the contralateral hand while subjects performed a choice reaction-time task. In Experiment 2, we stimulated over the hemisphere that was ipsilateral to the hand being used; the task was again a choice reaction-time task. In Experiment 3, we compared the effects of stimulation while subjects performed either a choice or a simple reaction-time task. We could thus determine whether delays in response time were due to the selection of responses.

Experiment 1. Contralateral stimulation

In this experiment, subjects were asked to carry out a choice reaction-time task, while being stimulated by TMS. The experiment was carried out to see if it was possible to prolong reaction times by stimulating over motor and premotor cortex contralateral to the hand being used.

Methods

Subjects

There were 10 subjects. Five used their right hand; of these, four were right handed (two male, two female) and one was left handed (male). Five used their left hand; of these there were four right-handed subjects (four male), and one left-handed subject (female). Handedness was measured using the Oldfield Handedness Inventory (Oldfield, 1971). Ethical permission for this study was obtained from the Central Oxford Research Ethics Committee (no. 94.261), and consent was obtained from all subjects in accordance with the declaration of Helsinki (BMJ 1991; 302: 1194).

Localizing motor cortex and premotor cortex

There are no obvious landmarks on the scalp that correspond to different cortical areas, and so we located the motor areas of interest with reference to the motor cortex. An initial estimate of the skull position over the hand representation in motor cortex was marked 4 cm lateral and 2 cm anterior to

Cz (EEG convention). Recording of muscle potentials was done via two electrodes taped over the flexor digitorum profundus. These were connected to a Medelec MS20 EMG machine. EMG readings were only taken while localizing motor cortex.

To locate the precise position of the fingers' representation in motor cortex, we searched to find a point of stimulation that resulted in the maximum motor evoked potential (MEP) with the minimum stimulation strength. A figure-of-eight stimulation coil (each wing 70 mm in diameter), connected to a Magstim 200 with maximum output of 2.0 T, was placed over the left or right motor cortex tangential to the skull, with the handle pointing backwards parallel with the midline. The coil's tangential orientation with respect to the head was ensured by placing a small piece of cork at one end. The intensity of stimulation was increased from 30% of maximum output in 5% steps until an MEP was just visible. The coil was then moved in 0.5-cm steps medial, lateral, posterior and anterior until the point of the maximum MEP was ascertained. Stimulation intensity was then decreased to the lowest setting at which MEPs could still be induced with all pulses. The coil was then moved in lateral, medial, posterior, and anterior steps of 0.5 cm to check that adjacent sites did not more reliably elicit MEPs on three trials. If no better site was found then the provisional site was taken to be the optimal position of stimulation of the finger representation in motor cortex—the 'hot spot'. If a better site was found then the procedure was repeated iteratively until the hot spot was identified. The minimum output required to get an MEP at the hot spot was recorded. The coil was then removed and a grid of points for stimulation was marked on the scalp.

The sites that were marked on the scalp were all measured relative to the hot spot. Three positions were marked 1, 2 and 3 cm anterior to the hot spot and at the same laterality; a further three positions were marked 1 cm medial to these. This formed a grid of reference (Fig. 1). The premotor (P) cortex site was located as the point 2 cm anterior and 1 cm medial to the hot spot. This was estimated from the location of the dorsal premotor cortex established in a PET study by Fink *et al*. (1997) (Fig. 1). Stimulation was also carried out over a site located 1 cm posterior and at the same laterality of the hot spot. A 'sensorimotor' (SM) site was also chosen. This was positioned 1 cm posterior to the motor hot spot. It is known from coregistration of TMS with MRI and PET scans that the motor hot spot is situated on the anterior lip of the central sulcus just anterior to the position of maximum change in regional cerebral blood flow during hand movement (Wassermann *et al*., 1996). The SM site chosen in this study should therefore be over the central sulcus. Stimulation over this site still induced MEPs. The SM site should also still be sufficiently distant from the P site for the effects of TMS over the two sites to be dissociable.

Task

During all the experiments, the subjects sat facing a PC (486) computer with their chin on an adjustable chin rest ~50 cm from the screen. The subjects placed their left or right hand on the table, and rested their index and middle fingers on two keys in front of them. The task involved responding with the middle or index finger according to the shape that was presented on the screen. The shapes were presented for 100 ms, and responses were timed from the moment of cue onset. If a small circle or a large rectangle was presented on the screen, the subjects responded with their index finger. If a large circle or small rectangle was presented, the subjects responded with their middle finger. Neither shape nor size alone determined the response required; by making the response selection process more difficult we ensured relatively long response times. The inter-trial interval was 4 s. The task is summarized graphically in Fig. 2.

The subjects were given two sets of 48 practice trials

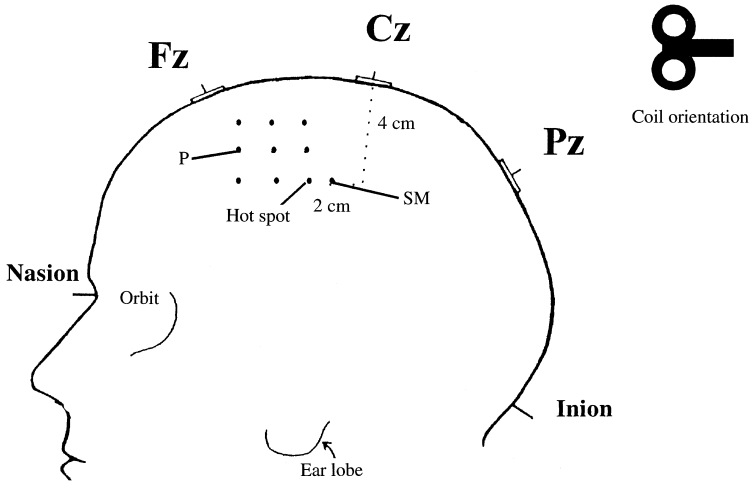

Fig. 1 Sites of stimulation and coil orientation. The hot spot was the site of lowest stimulation intensity for seeing an MEP in the hand muscles, and was ~4 cm lateral to Cz, and 2 cm anterior. The P site was over premotor cortex and was 2 cm anterior and 1 cm medial to the hot spot. The SM site was 1 cm anterior to the hot spot at the same laterality.

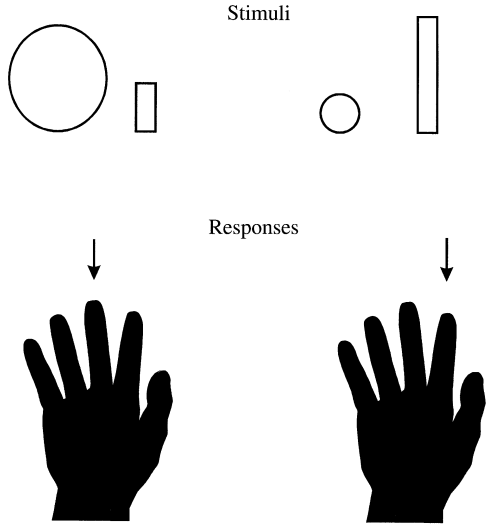

Fig. 2 Summary of the choice reaction-time task performed by the subjects. Just one of the four shapes was presented to the subjects on any trial. The subject was instructed to make a key press response with the middle finger whenever either the large circle or small rectangle (top left) was presented on the monitor screen. The subject was instructed to press another key with the index finger whenever either the small circle or large rectangle (top right) was shown. The stimuli were chosen to emphasize the selection component of the task; neither the size nor the shape alone of the instructing stimulus was sufficient to guide response selection.

without stimulation pulses. The subjects were first told which responses were correct, and during the first few practice trials they were given verbal feedback so as to ensure that they responded correctly. The subjects were encouraged throughout to be as quick and as accurate as possible. After two sets of 48 trials the response times and errors were briefly inspected, and the subjects were given a further 24 trials if their reaction times were still highly variable.

During the experiment, the subjects were magnetically stimulated over the hemisphere contralateral to the hand being used. The subjects performed the task in blocks of 12 trials. The subjects were stimulated for eight blocks at each site (P and SM). The order of sites that were tested was varied across subjects. For the P site, stimulation was first given at that site, but if there was no effect, tests were made at other sites within a circle with a radius of 1 cm centred on the P site. In early subjects, the search was less constrained although the site included in the results was always within 0.5 cm of the P site.

All stimulation was at 70–80% of stimulator output. This is the first reported study of the effects of TMS over the dorsal premotor cortex and it was not clear at the start of the investigation what would be an effective level of stimulation. It was not clear if an effective level of stimulation could be defined for each subject individually by reference to their flexor digitorium profundus hot spot threshold. This level was chosen high enough for us to be confident that we would not miss any potential experimental effect in false negative findings. It was felt that the use of a constant stimulation intensity would make the study replicable.

The subjects were stimulated on half of the trials, making a total of 288 experimental stimuli on a given test day. In each block of 12 trials, the subjects were stimulated once at six different intervals. The time of each magnetic stimulus was measured from the onset of the cues on the screen. The intervals were 140, 180, 220, 260, 300 and 340 ms. The stimulation and non-stimulation trials were presented in a random order. The subjects were first adapted to stimulation by slowly increasing the output of the stimulator from 50% in 5% steps. This block of trials was not included in the analysis. During the experiment, if the subject made less than seven correct responses on stimulation trials for any interval, a further two blocks were given. No more than 400 pulses were given to any subject on one day.

Analysis

All response times were recorded and stored on disk for later analysis. The incorrect responses were too few to analyse and were not used in the analysis of response times. The results were analysed using SPSS for Windows. The data were normalized: for each individual, we calculated the percentage change of the median response times with stimulation compared with the median response times with no stimulation. The percentage change is an indication of the effect of stimulation compared with the 'no stimulation' baseline. The 'no stimulation' values (0.0) could not be entered into a parametric analysis of variance (ANOVA). Friedman non-parametric ANOVAs for related samples were therefore used. These were followed up with single group *t* tests (Bonferroni corrected) on the response percentage changes, with a null hypothesis that there was no percentage change.

MRI scan

In a single subject, the motor hot spot and the P site were marked on the skull using a capsule containing garlic and soya oil. A T_1-weighted spin echo MRI scan was then taken on a Siemens Vision scanner operating at 2 T. On the scans shown in Fig. 3, a line was first drawn tangential to the surface of the skull. This represents the orientation of the stimulating coil. A line was then erected at 90° to indicate the centre of the area where the induced field was at its maximum. For the motor hot spot the line passes through the central sulcus. For the P site the line passes through the superior part of the precentral sulcus.

Results

Left hemisphere stimulation (right hand)

Median response times on the choice task ranged between 350 and 600 ms. The question of whether stimulation at the

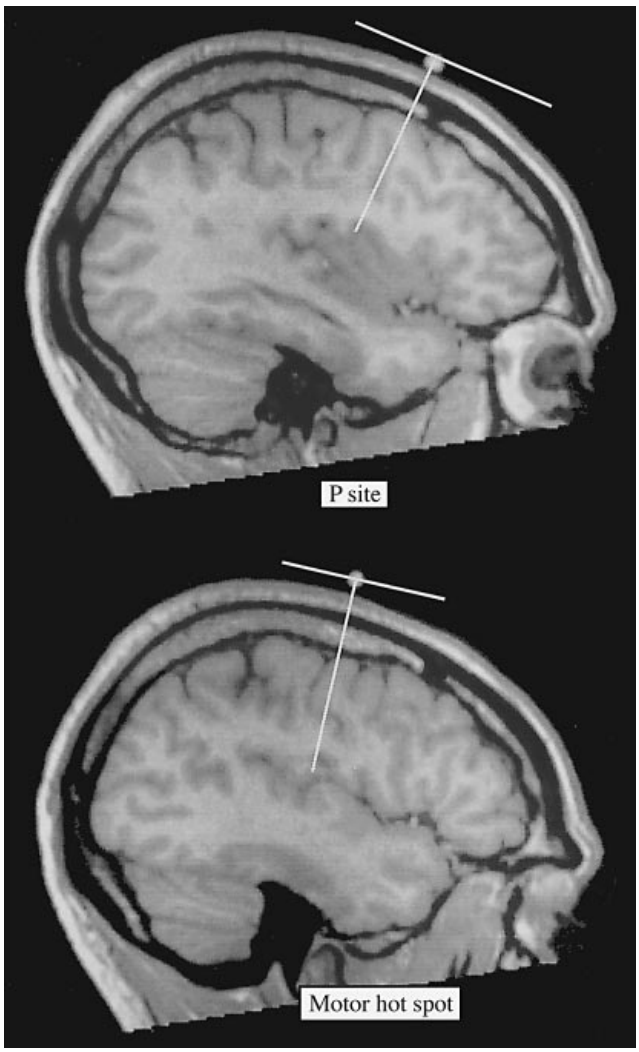

Fig. 3 The T-bars are superimposed on one subject's MRI scan to indicate the P site (above) and hot spot site (below) of stimulation. The bars were constructed by placing a line tangential to the skull at the point of stimulation and dropping a perpendicular into the grey matter. The P site was over the superior limb of the precentral sulcus and the hot spot was over the anterior bank of the central sulcus.

P and SM sites had a distinct effect was first addressed by comparing the results in a two-way repeated measures parametric ANOVA of the normalized reaction times on stimulation trials. The first factor was the site of stimulation, with two levels, P and SM. The second factor was the time interval after cue presentation at which stimulation occurred; this had six levels. There was no significant main effect of site of stimulation [$F(1, 4) = 0.14$, $P > 0.05$] or stimulation interval [$F(5, 20) = 2.08$, $P > 0.05$] but there was a significant interaction between the site and time of stimulation [$F(2, 10) = 4.38$, $P < 0.05$]. This suggests that TMS over the P site and SM sites had distinct effects.

The effect of stimulation over a P site was significant when examined using a repeated measures ANOVA [$\chi^2(6) = 13.52$, $P < 0.05$]. Further *t* tests were carried out at all the TMS stimulation intervals. The response time at the stimulation interval of 140 ms was significantly longer with stimulation than without stimulation ($P < 0.05$). The response times at a cue–stimulation interval of 300 ms were prolonged, but this was not significant when Bonferroni corrected (Fig. 4A).

For the SM site, the one-way repeated measures ANOVA revealed that the effect of stimulation interval approached significance [$\chi^2(6) = 10.86$, $P = 0.093$]. Subsequent *t* tests (Bonferroni corrected) found that at the intervals of 300 and 340 ms the prolongation of response time was significantly longer than the response times without stimulation ($P < 0.05$) (Fig. 4B). There were no significant delays at any other stimulation intervals.

Further paired *t* tests were carried out to compare the response times for the P and SM sites at stimulation intervals of 140, 300 and 340 ms. The response time at 140 ms was significantly longer for the P site than for the SM site ($P < 0.05$) (cf. parts A and B in Fig. 4).

Right hemisphere stimulation (left hand)

Stimulation over the P site was significant when examined using a repeated measures ANOVA [$\chi^2(6) = 14.74$, $P < 0.05$]. Therefore, *t* tests (Bonferroni corrected) were carried out at all the TMS stimulation intervals. The response time at a stimulation interval of 140 ms was significantly longer than for the 'no stimulation' condition ($P < 0.05$) (Fig. 5A).

For the SM site, the ANOVA revealed that the effect for stimulation interval approached significance [$\chi^2(6) = 11.14$, $P = 0.084$]. Subsequently, *t* tests were carried out at all the cue–TMS intervals. There were no significant differences; however, the response times at intervals of 300 and 340 ms approached significance ($P = 0.032$ and 0.049, respectively, before correction) (Fig. 5B). On this occasion the difference between response times for stimulation at 140 ms over P and SM sites did not reach statistical significance when they were compared directly with one another ($P > 0.05$).

Discussion

On a choice reaction-time task, TMS led to an increase in response times when applied over motor and premotor sites. The MRI scan (Fig. 3) indicates that the line of maximal stimulation at the motor hot spot passed through the central sulcus at the point at which it curves sharply. This probably represents the area which is expanded for the hand and arm representation (White *et al*., 1997; Yousery *et al*., 1997). At the more anterior site (the P site) the line of maximal stimulation passed through the superior limb of the precentral sulcus: at this point the sulcus is often complex with several side branches.

The increase in response time occurred when the pulse was delivered at a short interval over premotor cortex and at a longer interval over motor cortex. The effect of stimulation at the P site cannot be explained as artefactual. The visual cue lasted for only 100 ms and had already been displayed

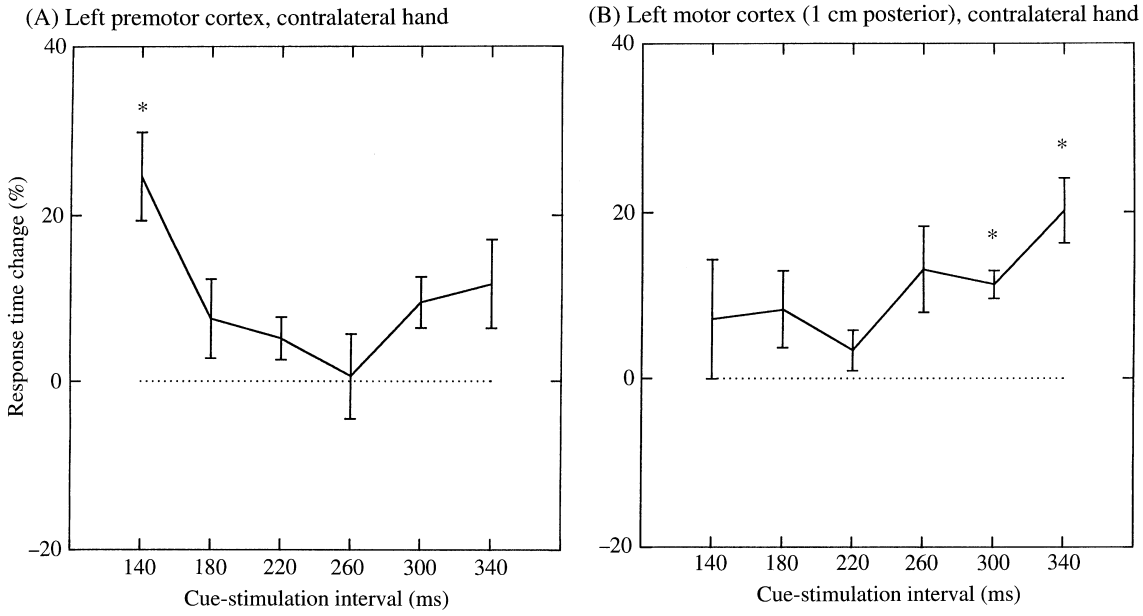

Fig. 4 The mean percentage change and standard errors in response time on the choice reaction-time task with stimulation. Each subject's median response time for each cue–stimulation interval was normalized by dividing by their non-stimulation response times. The resulting ratios are converted into percentage changes. The dotted line shows the prediction of the null hypothesis, that the stimulation has no effect on response time. **A** and **B** show the percentage changes in response time with stimulation over the left hemisphere while subjects performed a choice reaction-time task with their right hand; **A** and **B** show the results of stimulation at the P site and SM site, respectively. $*P < 0.05$.

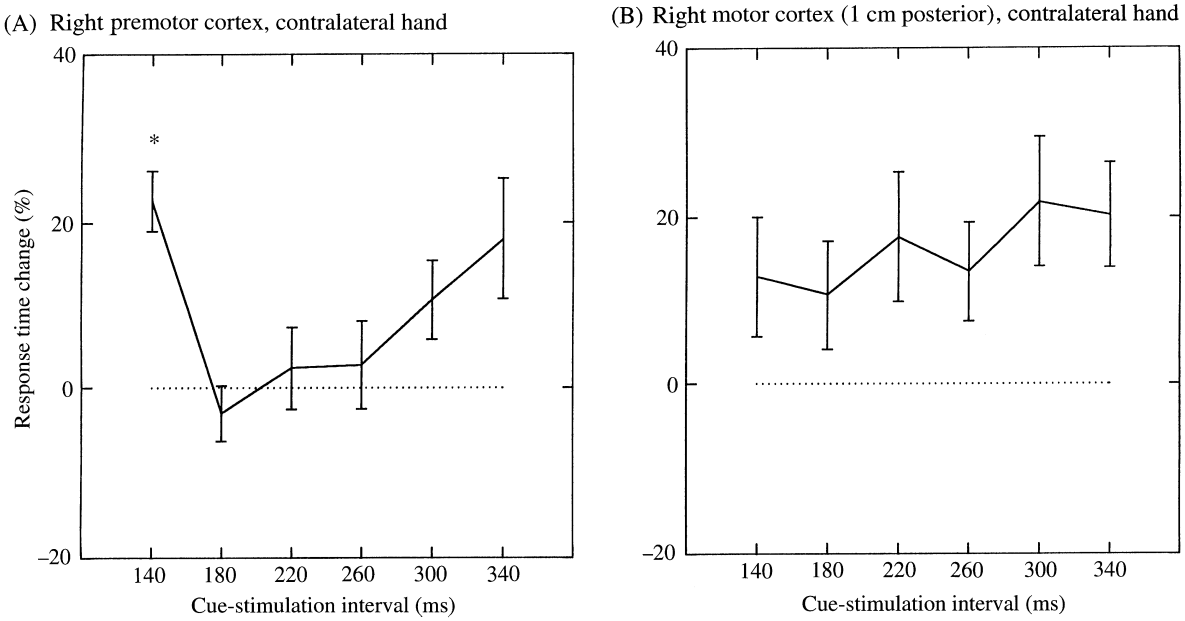

Fig. 5 The mean percentage change and standard errors in response time with stimulation over the right hemisphere while subjects performed the choice reaction-time task with their left hand; **A** and **B** show the results of stimulation at the P site and the SM site, respectively. $*P < 0.05$.

before the magnetic stimulation was given, so any blinks occurred after the cue had been switched off. The click caused by the stimulator might distract the subjects, but though there was a delay at 140 ms for the P site, no such delay was observed for the SM site. Finally, the stimulation could cause a slight jerk of the hand. This cannot explain why there was a delay at a short interval at the P site, but not at the SM site, even though the stimulation caused a larger movement of the hand over the SM site.

The increase in response times for stimulation at 140 ms over premotor cortex suggests a disruption of the process of response selection. The visual cue has already been turned off, and so stimulation does not interfere with seeing the shape. The motor response does not typically occur until a

further 250 ms or so. Selection of movement must occur some time after the visual cue has been recognized and before the onset of movement.

The effect at 140 ms at the P site cannot be explained in terms of disruption of movement execution. A high intensity pulse delivered over the motor 'hot spot' leads to an MEP followed by a silent period in the EMG trace (Day *et al*., 1989). This period can last as long as 150 ms. However, stimulation over the P site at 220 or 260 ms did not cause a significant delay in response time as would be expected if the effect at 140 ms was caused by an ensuing silent period in the EMG record.

However, the increase in response time for stimulation at 300 and 340 ms over the SM site is likely to be explained in terms of disrupting movement execution. Stimulation over the motor cortex only delayed responses when the stimulation occurred at intervals close to the onset of movement.

Experiment 2. Ipsilateral stimulation

The previous experiment was repeated with new subjects, but with stimulation over the hemisphere ipsilateral to the hand being used.

Method

Subjects

There were 15 subjects in all. Five subjects used their left hands; of these, all were right-handed (three male, two female). Five subjects used their right hands; of these, all were right-handed (four male, one female). A further five subjects responded with their left hand and right hand; of these four were right-handed (four male) and one left-handed (female). As before, handedness was measured using the Oldfield Handedness Inventory (Oldfield, 1971).

Search for an ipsilateral P site

The method was as in Experiment 1 but with stimulation of the hemisphere ipsilateral to the hand being used. However, it was important that a thorough search be made around the P site when negative results were obtained for the right hand. As well as testing the SM and P sites, we therefore marked eight different sites in a rectangle centred on the P site; these sites were 1 cm apart. Subjects were given four blocks of 12 stimuli at each site. If there was no effect, then the next site was stimulated; if there was an effect four more blocks were given.

An additional experiment was carried out in the right hemisphere. Five subjects were stimulated over the right hemisphere while performing the task with their contralateral hand. These same subjects were then tested with their ipsilateral hand, over a site which led to a delay for stimulation at an interval of 140 ms when the subjects used their contralateral hand. For these subjects, the stimulation intervals were 20, 60, 100, 140, 180 and 220 ms.

Results

Left hemisphere stimulation (left hand)

The stimulation over the P site was significant using a repeated measures ANOVA [$\chi^2(6) = 15.79$, $P < 0.05$]. Planned *t* tests (Bonferroni corrected) were carried out at all the TMS intervals. The response times at the stimulation interval of 140 ms was significantly longer ($P < 0.05$) (Fig. 6A).

For the SM site, the ANOVA showed that the effect for stimulation interval was not significant [$\chi^2(6) = 4.11$, $P = 0.66$]. A further paired *t* test showed that the response time at the P site at 140 ms was significantly longer than for the SM site at the same interval ($P < 0.05$) (cf. Fig. 6A and B with Fig. 4A and B). There was a significant difference between the effect of stimulation at 140 ms at the P and SM sites when they were compared directly ($P < 0.05$).

Right hemisphere stimulation (right hand)

The response times for the P site were not significant [$\chi^2(6) = 7.48$, $P = 0.28$, ANOVA]. Moreover, *t* tests were carried out at all intervals, and none were found to be significantly different from the stimulation versus 'no stimulation' condition (Fig. 7A).

The response times for stimulation over the SM site approached significance using a repeated measures ANOVA [$\chi^2(6) = 11.31$, $P = 0.079$]. Inspection of Fig. 7B shows that in general ipsilateral stimulation advanced, rather than slowed, responses. However, *t* tests revealed no significant differences at any interval.

Right hemisphere stimulation (left hand and right hand)

In this section we report the effect on the ipsilateral hand of stimulating at the P site shown to be effective for disrupting the contralateral hand (see Experiment 1, right hemisphere stimulation and left hand performance, Fig. 5A). When the same subjects used their right hand, with stimulation at the same site, there were no significant effects of stimulation at any stimulation interval [$\chi^2(6) = 1.89$, $P = 0.93$] (Fig. 11). However, one of the five subjects, a right-handed male, did show a small increase in response time for stimulation versus no-stimulation at 100 and 140 ms.

Discussion

The results of this experiment suggest an asymmetry. Stimulation of the left hemisphere at a P site at 140 ms delayed response times with the left hand, but stimulation over the right hemisphere had no effect. This was the case

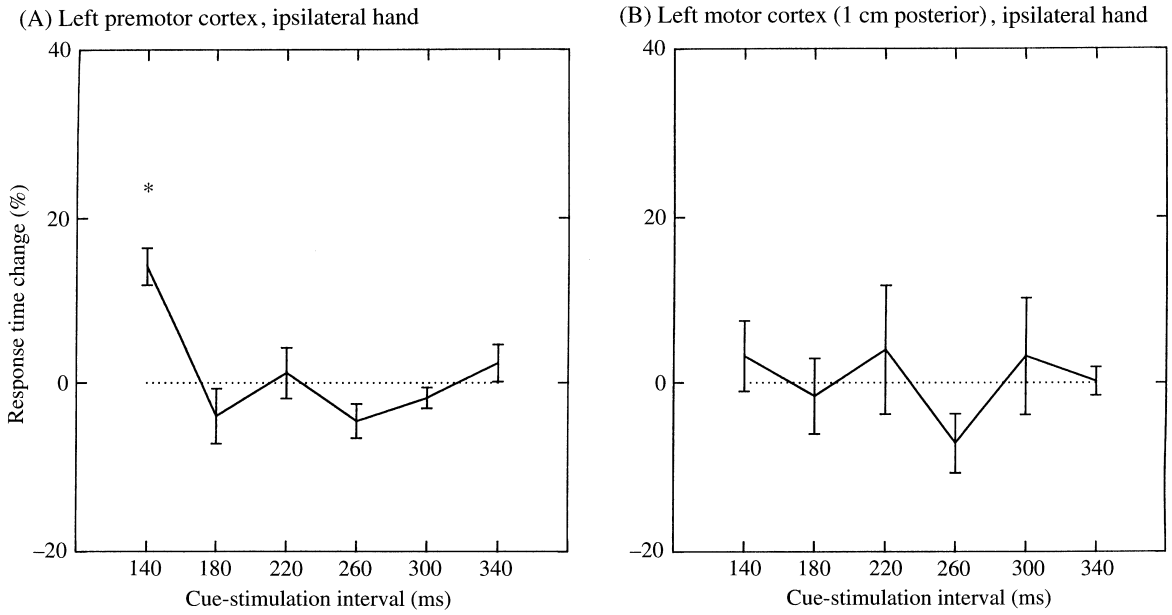

Fig. 6 The mean percentage change and standard errors in response time for stimulation over the left hemisphere while subjects perform the choice reaction-time task with their left hand; **A** and **B** show the results of stimulation at the P site and the SM site, respectively. *$P < 0.05$.

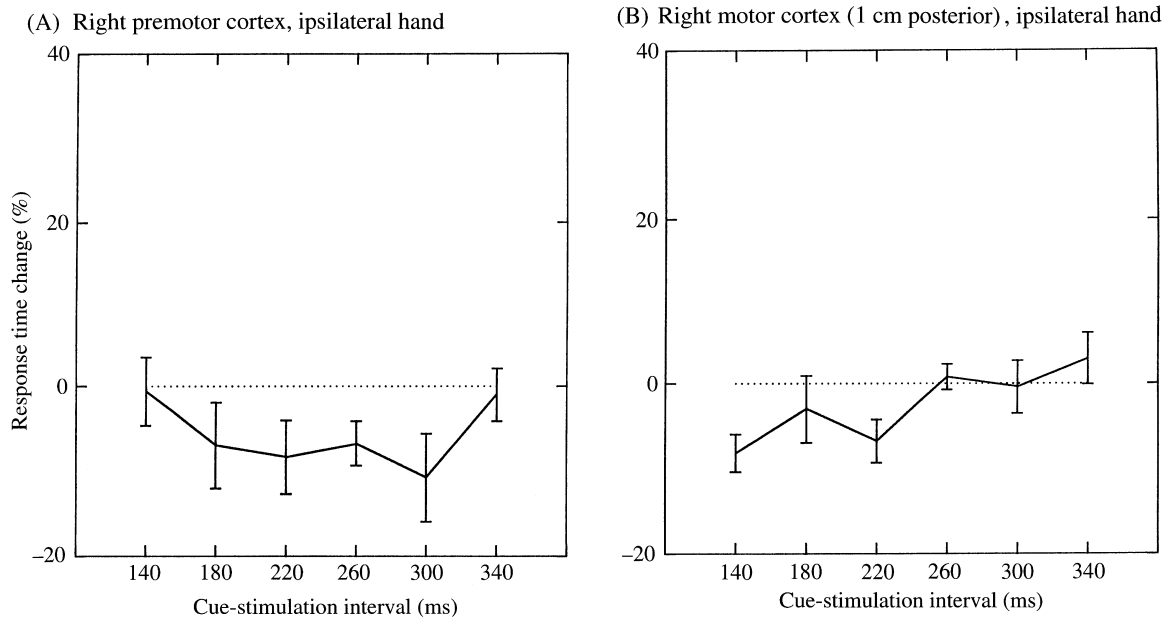

Fig. 7 The mean percentage change and standard errors in response time for stimulation over the right hemisphere while subjects perform the choice reaction-time task with their right hand; **A** and **B** show the results of stimulation at the P site and the SM site, respectively.

even though we searched the right hemisphere systematically to see if an effect could be detected.

For right hemisphere stimulation there was a slight but non-significant advancement of the response for the right hand between 180 and 300 ms (Fig. 6A). This phenomenon has been observed in other TMS studies (Pascual-Leone *et al.*, 1992). This phenomenon may be part of every experiment and any delays observed are superimposed on a small advancement of reaction.

In the discussion of Experiment 1 we argued that the delay caused by stimulation over the P site was not artefactual. The results of the present experiment increase our confidence in this conclusion. If blinks or clicks were responsible, it would not be possible to explain why the results were asymmetrical. Furthermore, no induced movements were observed in the ipsilateral hand as the result of stimulation of the P or SM sites. This may account for the lack of effect of stimulating over motor cortex in the present experiment.

Experiment 3. Choice versus simple reaction times

The aim of the final experiment was to investigate whether the delays observed when stimulating at 140 ms over premotor cortex reflect interference with a process of response selection. The subjects were given both a choice reaction-time task and a simple reaction-time task.

When testing response times on the simple reaction-time task, it was important to avoid the effects of either evoked hand movements or the silent period in the EMG. Given short response times, it would not be possible to tell whether a delay for stimulation at the P site was the consequence of these effects. We therefore measured the effects of stimulation on the ipsilateral hand, since in Experiment 2 no movements were induced and no delays were caused by stimulation of the motor cortex ipsilateral to the responding hand.

There is another problem concerning TMS during a simple reaction-time task. The click or tap sensation caused by the stimulation can act as a stimulus to movement. As a control, we therefore also stimulated over Pz (10–20 EEG convention). This site was chosen because stimulation over Pz did not induce any movements.

Since we found a delay when stimulating over the left premotor cortex, we also stimulated over the left motor cortex on the simple reaction-time task. This would show whether any effect found on the simple reaction-time task was specific to the premotor cortex.

Methods

Subjects

There were 10 subjects. Five responded with their left hand; all were right-handed (four male, one female). The other five subjects have already been mentioned in Experiment 2. As described there, they were stimulated over their right cortex and both hands were tested. Their data for the choice reaction-time task have already been reported in Experiment 2. Of these subjects, four were right-handed (male) and one left-handed (female). As before, handedness was measured using the Oldfield Handedness Inventory (Oldfield, 1971).

Tasks

The choice reaction-time task was as used for Experiments 1 and 2. In the simple reaction-time task, the subjects saw the same visual cues as in the choice paradigm, but the responses required were different. Subjects were asked to respond to all the cues by pressing a response key with their first finger. This is shown diagrammatically in Fig. 8. The shapes were presented for ~100 ms, and responses were timed from the moment of cue onset. The inter-trial interval varied from 4 to 6 s. The inter-trial interval was randomized to prevent subjects anticipating the visual cue. The subjects were given two practice sets of 48 trials without stimulation.

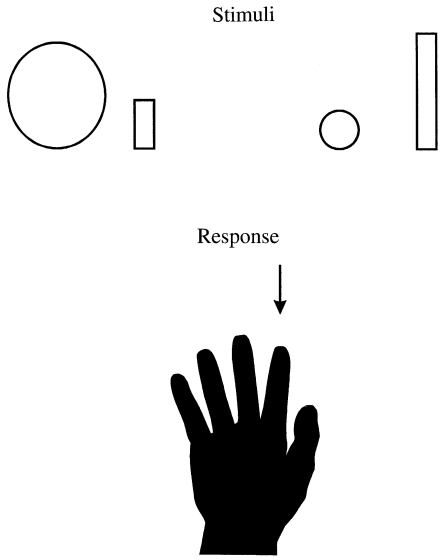

Fig. 8 Summary of the simple reaction-time task performed by the subjects. Just one of the four shapes was presented to the subjects on any trial. The same four shapes were used in the choice task (Fig. 2) and the simple task. The subject was instructed to make the same index finger key press response on every trial when any of the shapes were presented on the monitor.

The subjects were stimulated for eight blocks of 12 trials at each site.

Site

For the subjects using their left hand, the P site was identified as described for Experiment 2. For the subjects using their right hand, the procedure was as described for the last group of subjects in Experiment 2. The same P sites were used for the choice and simple task, with the choice task being given before the simple task. The stimulation intervals used in the choice and simple tasks were 20, 60, 100, 140, 180 and 220 ms.

For the simple task, stimulation was given over the P site and over Pz (10–20 EEG convention). In addition we stimulated over the motor cortex while subjects performed the simple task with their left hand.

Results

Left hemisphere stimulation (left hand): choice versus simple task

For the choice reaction-time task, a repeated measures ANOVA revealed a significant effect of stimulation [$\chi^2(6) = 16.61$, $P < 0.05$]. Therefore t tests (Bonferroni corrected) were carried out at all the stimulation intervals. The response time at 100 ms was significantly longer ($P < 0.01$) (Fig. 7). The response time at the stimulation interval of 140 ms was also increased, but the difference was no longer significant after Bonferroni corrections (Fig. 9).

For the simple reaction time, the ANOVA revealed a

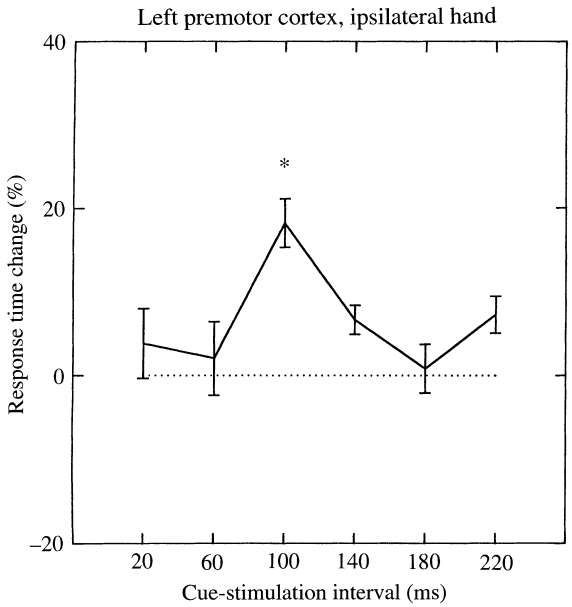

Fig. 9 The mean percentage change and standard errors in response time for stimulation over the left hemisphere P site while subjects perform the choice reaction-time task with their left hand. *$P < 0.05$.

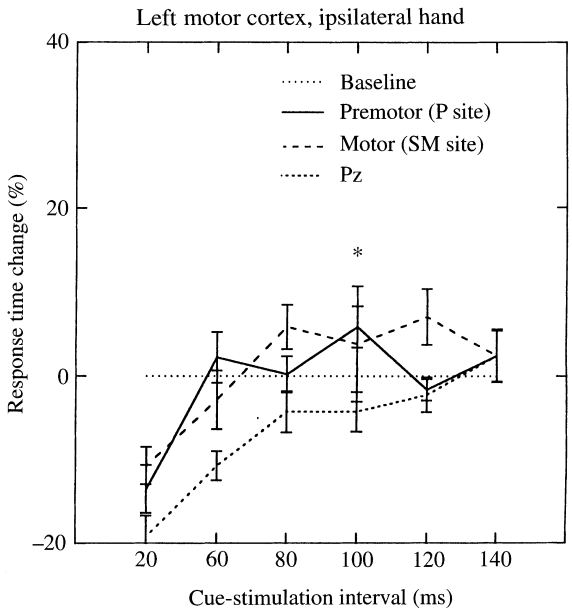

Fig. 10 The mean percentage change and standard errors in response time for stimulation over the left hemisphere while subjects perform a simple reaction-time task with their left hand. The solid line is for stimulation over the P site as in Fig. 9. The long dashed line is for stimulation over the SM site, and the small dashed line is for stimulation over Pz. The dotted line shows the prediction of the null hypothesis, that the stimulation has no effect on response time. *$P < 0.05$.

significant effect of stimulation at the P site [$\chi^2(6) = 16.99$, $P < 0.01$], SM site [$\chi^2(6) = 16.82$, $P < 0.01$] and Pz site [$\chi^2(6) = 20.52$, $P < 0.01$]. When *t* tests were carried out, there was a significant advancement at 20 ms for the Pz and SM sites ($P < 0.05$); there was an advancement at the P site but this was not significant. In addition, the response time at the Pz site was advanced at a stimulation interval of 60 ms ($P < 0.05$).

At an interval of 100 ms, stimulation over the P site resulted in slower response times than stimulation over Pz ($P < 0.05$) (Fig. 10). However, there was no significant difference between the response times for the P and SM site at any cue–stimulation interval.

Right hemisphere stimulation (right hand): choice versus simple task

For the choice reaction-time task, when subjects used their right hand there were no significant effects at any stimulation interval [$\chi^2(6) = 1.89$, $P = 0.93$]; this result has already been mentioned above in Experiment 2—right hemisphere left hand (Fig. 11).

For the simple reaction-time task, the ANOVA revealed a significant effect of stimulation at the P site [$\chi^2(6) = 15.94$, $P < 0.05$] and Pz site [$\chi^2(6) = 18.17$, $P < 0.01$]. Later *t* tests showed that the response times were significantly advanced for the Pz site at 20 ms ($P < 0.05$); there was a similar advancement for the P site, but the difference did not survive the Bonferroni correction. None of the response times for the P site were significantly different from the times for the Pz site (Fig. 12).

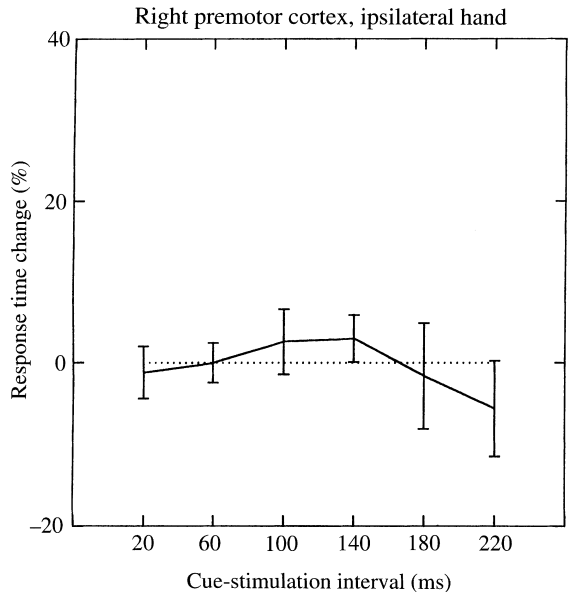

Fig. 11 The mean percentage change and standard errors in response time for stimulation over the right hemisphere P site while subjects perform the choice reaction-time task with their right hand.

Discussion

Stimulation over the left P site at 100 ms resulted in an increase in the response time on the choice reaction-time task. In Experiment 2 the effect occurred at 140 ms, but no stimulation was carried out at the earlier interval of 100 ms.

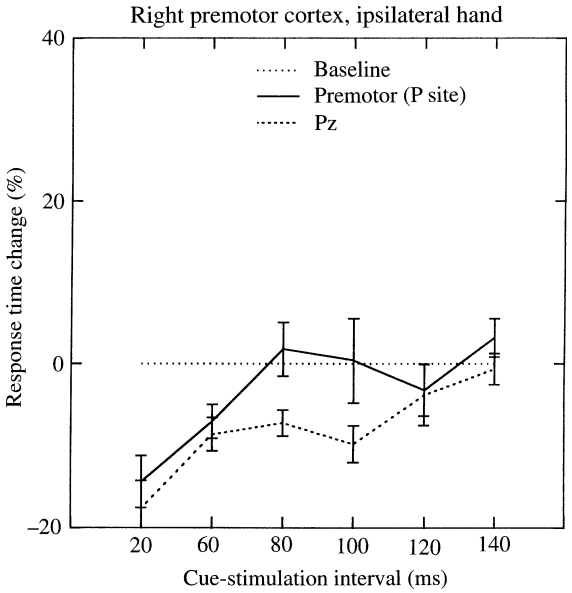

Fig. 12 The mean percentage change and standard errors in response time for stimulation over the right hemisphere while subjects perform a simple reaction-time task with their right hand. The solid line is for stimulation over the P site and the small dashed line for stimulation over Pz. The dotted line shows the prediction of the null hypothesis, that the stimulation has no effect on response time.

In the present experiment there was a tendency for a delay at 140 ms, but the difference did not survive the Bonferroni correction.

In the simple reaction-time task, there was an advancement for both hands at the shortest interval. Either the click or the tap sensation produced by the stimulator could have acted as a salient 'go' stimulus. Pascual-Leone *et al*. (1992) have reported that responses to auditory signals were faster than responses to visual stimuli.

There is no clear evidence of a differential effect of stimulation at the P site on the simple reaction-time task. For the left hemisphere, stimulating at the P site delayed the choice reaction time. On the simple reaction-time task for the left hand, the response time for the P site was longer when compared with that for the Pz site, but not when compared with that for the M site at 100 ms. This result is difficult to interpret. There was the same delay at 100 ms for the right hemisphere when comparing the P with the Pz site on the simple reaction-time task; yet, for this hand, stimulation at the P site caused no effect on the choice reaction-time task. This suggests that the delay observed in the left hand at 100 ms is not due to the disruption of the processes interfered with on the choice reaction-time task. Furthermore, the effect at the P site on the choice reaction-time task was much larger than the effect on the simple reaction-time task, and on the choice reaction-time task the effects are significantly different for the P and SM sites (Experiment 2, Fig. 5).

We conclude that the marked delay on the choice paradigm at the P site probably reflects an interference with response selection. The results of experiments 2 and 3 further suggest that the left premotor cortex plays a dominant role in the selection of responses.

General discussion

Premotor cortex and selection of movements

We have argued that stimulation over the dorsal premotor cortex can temporarily interfere with the selection of movements that are instructed by visual cues. These results confirm earlier studies in which it was shown that lesions in premotor cortex disrupt the selection of responses to visual cues in monkeys (Halsband and Passingham, 1985; Petrides, 1987) and in patients (Halsband and Freund, 1990). More recently, Kurata and Hoffman (1994) used muscimol to interfere temporarily. They found that interference with dorsal premotor cortex, but not ventral premotor cortex, caused the monkeys to make directional errors on a task in which visual cues instruct different movements.

Studies of signal- and set-related activity in premotor cortex have found that many of the units have firing patterns that are directional or selective. Weinrich *et al*. (1984) reported that 59% of the signal-related cells and 52% of the set-related cells were directionally specific, suggesting that they were coding specific movements on the basis of the visual cues. Wise *et al*. (1992) showed that the majority of these cells specified the response rather than the nature of the visual cue. Boussaoud and Wise (1993) used the same stimuli in different contexts, and found that 55% of premotor cells cued a limb action rather than a spatial location. Finally, Mitz *et al*. (1991) have found a substantial population of cells which showed learning-dependent changes in activity on a visual conditional task. These findings support the hypothesis that the dorsal premotor cortex is involved in the selection of motor responses on the basis of visual cues.

This is, to our knowledge, the first report of the effect of TMS over the dorsal premotor cortex. More medial stimulation over the supplementary motor area has been shown to disrupt the sequences of memory guided saccadic eye movements (Muri *et al*., 1994, 1995) and, in some situations, hand movements (Cunnington *et al*., 1996; Gerloff *et al*., 1997). Ro *et al*. (1997) have recently shown that stimulation with a circular coil over the frontal lobe slows the selection of saccades into the contralateral hemispace when they are cued by a central arrow. The same stimulation does not disrupt contralaterally directed saccades made to an asterisk flashed at the target position. The results of Ro *et al*. (1997) are analogous to the current finding; the TMS disrupts the selection of a response, whether it is made with the hand or with the eyes, when its selection is governed by an arbitrary learned association with a cue. The crucial stimulation site for saccade disruption could not be precisely identified by Ro *et al*. (1997). The results are nevertheless consistent with parallel mechanisms for the selection of hand and eye movement responses which, in the monkey, are associated

with the dorsal premotor cortex and the supplementary eye field (Passingham, 1993; Wise, 1996).

Spatial location

The advantage of using temporary interference is that it is possible to dissociate effects occurring at different spatial locations and at different times. The MRI scan showed that the effect of stimulation over the P site was maximal over the superior limb of the precentral sulcus. In a PET experiment, Fink *et al*. (1997) mapped the motor and premotor areas, and identified activation in the dorsal premotor cortex. The SM site lay 1 cm behind the motor 'hot spot', and the MRI indicated that the effect of stimulation at the motor 'hot spot' was maximal over the point at which the central sulcus is 'knob' shaped. White *et al*. (1997) and Yousry *et al*. (1997) suggest that the forelimb is mapped to this point in the central sulcus. Stimulation over the P site induced effects at different times from those with stimulation over the SM site. Over premotor cortex, pulses at short stimulation intervals prolonged responses, whereas this was true for pulses at long intervals over sensorimotor cortex.

Neurophysiological studies carried out on premotor and motor cortex in monkeys have found that there is a pattern to the distribution of cells in areas 6 and 4 that fire in relation to a visual cue or movement of a limb. These studies suggest that cells that are modulated by the visual signal are more abundant in more anterior positions. Weinrich *et al*. (1984) found an increasing percentage of cells showed signal-related activity the further anterior to the central sulcus they recorded. The greatest proportions of the signal- or set-related cells were recorded in area 6, 1–1.5 cm anterior to the central sulcus, but movement-related cells were more evenly distributed throughout areas 4 and 6. Johnson *et al*. (1996) found that a greater percentage of cells anterior to the area 4–area 6 border were signal- or set-related than cells at a more posterior location; movement-related cells were more abundant in posterior positions. Okano (1992) found that 22% of premotor cortex neurons showed signal-related activity, and this compared with 0% of motor cortex neurons.

Latency

Stimulation over premotor cortex interfered with response times when applied at between 100 and 140 ms after presentation of the visual cue. It is important to take into account the fact that the effects of magnetic stimulation last beyond the time of stimulation. However, the delay was not significant when stimulation was applied at 180 ms.

Weinrich *et al*. (1984) reported that on a visual conditional task the mean onset of signal-related units in the premotor cortex was 138 ms after the instruction stimuli. This was true even though the delay between the instruction stimulus and the 'go' signal varied between 600 and 2100 ms. Johnson *et al*. (1996) reported that the mean onset of cell activity after an instruction stimulus was 166 ms, but this was an average for recording taken from both area 6 and area 4. Weinrich *et al*. (1984) found that the movement-related units in premotor cortex showed activity changes with a mean time of 137 ms before the onset of movements, whereas for the precentral motor units the comparable mean time was 83 ms.

The increase in response time when stimulating over the SM site occurred only when the magnetic stimulation was applied much closer to the movement. Day *et al*. (1989) have also shown that the onset of movement to a visual cue can be delayed by stimulating close to movement time. Pascual-Leone *et al*. (1992) have also shown a prolongation of reaction times when magnetic pulses of supra-threshold intensity were delivered close to voluntary muscle movements.

Crammond and Kalasaka (1996) have reported that, during reaching movements, cells in the motor cortex showed increased directionally tuned activity prior to, and during, movement. On the other hand, the activity of premotor cells was mainly restricted to the behavioural reaction time before the onset of movement. The authors point out that these results suggest that the motor cortex differs from the premotor cortex in exercising moment-to-moment control of the motor output.

Stimulation of the left premotor cortex at 300 ms also delayed response times with the right hand (Fig. 3A). This could result from interference with movement-related cells in premotor cortex (Weinrich and Wise, 1982; Camminiti *et al*., 1991; Kurata, 1993; Johnson *et al*., 1996). Alternatively, the delay may result from supra-threshold stimulation of motor cortex; high intensity stimulation over premotor cortex is sufficient to induce an MEP and silent period in motor cortex.

Left hemisphere dominance

The results from these experiments show that the left premotor cortex is dominant, and the dominance is for the selection of movements. Stimulation of the left premotor cortex (Experiment 2) delayed both the right and the left hand when subjects performed a selection task. Stimulation of the right hemisphere only delayed responses with the left hand. This pattern of dominance is similar to that observed in apraxia, where left hemisphere lesions disrupt performance with the ipsilateral hand but right hemisphere lesions do not (Harrington and Haaland, 1992; Kimura, 1993; Rushworth *et al*., 1998). Halsband and Freund (1990) reported that four patients with right premotor lesions were poor at learning to associate gestures with visual cues, even though they used their right hand. However, these authors tested the subjects on the learning of the associations, and it is possible that both premotor areas are involved when these tasks are being learned.

Kim *et al*. (1993) found that ipsilateral motor cortex was active when subjects performed a sequential finger tapping task, but only when the subject used their left hand. However,

they do not comment on activity in non-primary motor areas. Haaland and Harrington (1996) have reviewed imaging studies, and they point to a lack of studies reporting dominance in the motor system. However, in a recent PET study, Iacoboni *et al*. (1996) tested subjects on a choice reaction-time task in which the choice was between responses with the left or right hand. They found that the left premotor cortex was activated but not the right; however, the right premotor cortex was activated at a lower threshold of significance. Furthermore, Krams *et al*. (1998) have tested subjects while they prepared to move one of four fingers as instructed by the image of a hand. The left premotor cortex, but not the right, was activated whether the right or left hand (M. F. S. Rushworth *et al*., unpublished observations) was used.

It is not clear by what mechanism the left premotor cortex exerts dominance over the right premotor cortex. It has previously been shown that TMS can have an effect on the ipsilateral hand muscles, inducing both MEPs and silent periods (Wassermann *et al*., 1994). It is clear that inhibition is important in interhemispheric interactions; the normal MEPs or silent periods produced by contralateral stimulation are reduced if a conditioning pulse is applied to the ipsilateral hemisphere 10–20 ms before the contralateral stimulation is applied (Netz *et al*., 1995; Schnitzler *et al*., 1996). This interhemispheric inhibition is mediated by the corpus callosum; it was absent in a patient with callosal agenesis (Schnitzler *et al*., 1996). There is an asymmetry in the effects of inhibitory conditioning pulses over the two hemispheres; stimulating the left hemisphere in right handers has a greater effect than vice versa (Netz *et al*., 1995). It is possible that the dominance of the left premotor cortex may also be mediated by callosal connections, and stimulation of the left premotor cortex may have a greater inhibitory effect on the right premotor cortex than vice versa.

The pattern of dominance

Language is primarily controlled by the left hemisphere. This is in contrast to the pattern of dominance suggested by this study where stimulation of the right hemisphere clearly slows the responses of the contralateral hand. However, the dominance suggested by this study is analogous to the pattern shown for attention to the two visual fields. Corbetta *et al*. (1993) have shown, using PET, that the right parietal cortex is activated whichever side a visual stimulus is presented, whereas the left parietal cortex is mainly activated when a stimulus is presented in the right contralateral visual field.

The difference in the pattern of dominance for speech may be due to the fact that, whereas there are two hands and two visual fields, there is only one larynx and tongue. It is possible that a single organ is most efficiently controlled by a single hemisphere (Passingham, 1981). The delay in callosal conduction times may cause an inefficiency in co-ordinating rapid movements if they are controlled by both hemispheres (Ringo *et al*., 1994). In song birds, the songs are controlled by a single hemisphere (Nottebohm, 1977). In a recent paper (Hamdy *et al*., 1998), it has been shown that the cortical topography of the human oral, pharyngeal and oesophageal musculature is bilateral. However, the hemispheric asymmetry is independent of handedness. Swallowing movements are stereotyped, and they are not preferentially controlled by either hemisphere. To coordinate the muscles on both sides of the oesophagus it may be advantageous to control them primarily from one hemisphere alone. In the experiments presented in this paper the responses are arbitrary, and are learned hand movements. The selection of the muscles used in swallowing is not arbitrary and is always the same; this may explain why hemispheric asymmetry is not left-dominant, but is independent of handedness.

The question then arises as to why the dominance for rapid selection of limb responses maps to the same hemisphere as dominance for speech. One possibility, as suggested by Kimura (1993), is that speech evolved from a gesture system. The results from this experiment suggest that the left hemisphere's specialization is for the rapid selection from different alternative responses, whether manual or oral.

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