

Transcranial Magnetic Stimulation of Primary Motor Cortex Affects Mental Rotation

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Neuroimaging studies have shown that motor structures are activated not only during overt motor behavior but also during tasks that require no overt motor behavior, such as motor imagery and mental rotation. We tested the hypothesis that activation of the primary motor cortex is needed for mental rotation by using single-pulse transcranial magnetic stimulation (TMS). Single-pulse TMS was delivered to the representation of the hand in left primary motor cortex while participants performed mental rotation of pictures of hands and feet. Relative to a peripheral magnetic stimulation control condition, response times (RTs) were slower when TMS was delivered at 650 ms but not at 400 ms after stimulus onset. The magnetic stimulation effect at 650 ms was larger for hands than for feet. These findings demonstrate that (i) activation of the left primary motor cortex has a causal role in the mental rotation of pictures of hands; (ii) this role is stimulus-specific because disruption of neural activity in the hand area slowed RTs for pictures of hands more than feet; and (iii) left primary motor cortex is involved relatively late in the mental rotation process.

Introduction

In many situations where one object must be oriented properly relative to another, people physically rotate the object until it is in the appropriate orientation. Remarkably, people can perform these reorientation tasks even when no overt movement is allowed. In one standard experimental task, two objects – one of which is a rotated version of the other – are shown on a computer screen; participants determine whether the two objects are the same or mirror images of each other. One of the most consistent findings is that during such tasks objects appear to move along continuous trajectories, as they would during physical rotation; in fact, when stimuli must be rotated greater amounts, more time is required (Shepard and Cooper, 1982). Because the stimulus does itself not rotate during the task, this phenomenon has been referred to as *mental rotation* and is thought to involve the gradual transformation of visual mental images (Kosslyn, 1994).

Although visual perceptual mechanisms are involved in mental rotation (Shepard and Cooper, 1982), several lines of evidence indicate that motor mechanisms play a key role as well, at least when body parts are being rotated. The general idea is that mental rotation occurs when people imagine what they would see if they executed a particular action (Kosslyn, 1994). First, consistent with this idea, a number of behavioral studies have shown that it is easier to judge the handedness of limbs (whether they belong to the left or right side of the body) when they are oriented in ways that are compatible with the constraints imposed by their joints (Cooper and Shepard, 1975; Sekiyama, 1982; Parsons, 1987, 1994). Several other behavioral findings have also implicated motor processes in at least some forms of mental rotation (Georgopoulos and Massey, 1987; Pellizzer and Georgopoulos, 1993; Wexler *et al.*, 1998). For example, physically rotating a dial interferes with mental rota-

tion in the opposite direction, and such interference is greater when the speeds are similar (Wexler *et al.*, 1998). Second, the pioneering studies in nonhuman primates by Georgopoulos and his colleagues (Georgopoulos *et al.*, 1989) revealed that the primary motor cortex is involved in the mental rotation of body parts. In these studies, monkeys were trained to move one arm at various angles relative to a visual cue, which requires the internal computation of the final position of the arm. During the interval between the onset of the cue and the arm movement, the direction coded by a 'population vector' (which shows the intended movement direction encoded by an ensemble of neurons) shifted orientation incrementally over time, from the direction of the visual cue toward the direction of the required movement. Third, neuroimaging studies have shown that mental rotation and implicit movements of hands activate several brain regions involved in the visuomotor control of hand movement (Lang *et al.*, 1994, 1996; Bonda *et al.*, 1995; Parsons *et al.*, 1995; Porro *et al.*, 1996; Kosslyn *et al.*, 1998; Parsons and Fox, 1998), including the cerebellum, posterior parietal cortex, premotor cortex, supplementary motor cortex, and in some cases primary motor cortex. In sum, these convergent findings are good evidence that visuomotor and motor processes are involved in the mental rotation of hands, and presumably of other body parts. There is also evidence that motor processes may, at least sometimes, be involved in the mental rotation not only of body parts, but of other objects as well (Wexler *et al.*, 1998; Wolschlagel and Wolschlagel, 1998).

None of the previous research has shown, however, that motor processes play a causal role in such mental rotation. It is possible that motor processes are only incidentally activated by other, nonmotor processes, and that the real work of mental rotation is being conducted elsewhere in the brain. In addition, there has been controversy about whether primary motor cortex is involved in motor imagery and mental rotation since some studies found evidence for such an involvement (Lang *et al.*, 1994, 1996; Abbruzzese *et al.*, 1996; Erslund *et al.*, 1996; Porro *et al.*, 1996; Schnitzler *et al.*, 1997; Kosslyn *et al.*, 1998) while others did not (Rao *et al.*, 1993; Decety *et al.*, 1994; Leonardo *et al.*, 1995; Stephan *et al.*, 1995; Parsons and Fox, 1998), or found only weak evidence (Sabbah *et al.*, 1995; Hodge *et al.*, 1996; Roth *et al.*, 1996). If primary motor cortex plays a causal role in the mental rotation of pictures of hands (as opposed to being activated by other areas that in fact are doing the work), then disruption of its neural activity should interfere with task performance – and result in slower reaction time (RTs) or higher error rates. We produced transient disruption of neural activity by delivering single transcranial magnetic stimulation (TMS) pulses to the hand area in the left primary motor cortex. We focused on the left hemisphere because a recent positron emission tomography (PET) study with the same hand stimuli and mental rotation task used here (Kosslyn *et al.*, 1998) found

activation in left motor cortex. Moreover, several studies have documented that the left hemisphere has a predominant role in the planning and execution of both contralateral and ipsilateral movements. For example, in one functional magnetic resonance imaging (fMRI) study researchers found activation in left motor cortex during both contralateral and ipsilateral movements, but found activation in right motor cortex only during contralateral movements (Kim *et al.*, 1993). Furthermore, whereas repetitive TMS over right motor cortex interferes primarily with the execution of contralateral movements, repetitive TMS over left motor cortex interferes with the execution of both contralateral and ipsilateral hand movements, especially complex ones (Chen *et al.*, 1997a,b). A recent study (Fadiga *et al.*, 1999) also reported a clear pattern of lateralization during a motor imagery task: the MEPs elicited by a TMS pulse delivered to right motor cortex were larger only in the contralateral hand while they were larger in both ipsilateral and contralateral hands when the pulse was delivered to left motor cortex.

If the mental rotation of pictures of hands relies on the same neural structures recruited during overt movements and motor imagery, we should observe a high degree of specificity in the pattern of effects: stimulation of the hand area should disrupt mental rotation of pictures of hands but not, or to a lesser degree, of feet. To test this prediction we included a condition in which the participants mentally rotated pictures of feet.

Finally, disruption of neural activity should have an effect on performance only if it occurs during the time when the affected neural population is actually required to perform the task. Based on magnetoencephalographic (MEG) findings (Kawamichi *et al.*, 1998), we expected the motor cortex to be recruited rather late in the task, after earlier visuospatial encoding processes occurring in occipital and parietal areas. We tested this prediction by delivering the single TMS pulses at two latencies, relative to stimulus onset (i.e. interstimulus intervals, ISI): 400 and 650 ms.

Materials and Methods

Subjects

Ten right-handed [according to the Edinburgh Inventory (Oldfield, 1971)] volunteers (five males and five females) received \$40 for participation. They ranged in age from 22 to 32 years. All had normal neurological and physical exams and met currently recommended safety guidelines for TMS (Wassermann, 1998). None had any chronic illnesses or was taking any prescription medications. None had a history of unexplained spells or seizures, a family history of epilepsy, an implanted pacemaker or medication pump, or metal in the head other than dental fillings. The female volunteers were certain that they were not pregnant. Each subject gave informed consent prior to the study that was approved by the local Investigational Review Board, and none were aware of the purposes or the hypotheses at the time of testing. All subjects understood the instructions without difficulty.

Stimuli

A pair of pictures of hands (or feet, as appropriate) was used on each trial; the stimulus on the left side of each pair was always a left hand (or foot) presented upright, while the stimulus on the right side was a left hand (or foot) half of the time and a right hand (or foot) the other half of the time. The stimulus on the right appeared at orientations ranging from 20° to 140°, in increments of 40°. We anchored the left side of the stimulus with the left hand (or foot) to avoid visuomotor interference, which might have occurred if the left hand (or foot) had appeared on some trials on the right side of the screen. As illustrated in Figure 1, to minimize practice effects, four different finger configurations were used; for each finger configuration two versions were created, one with the palm facing forward and the other with the back of the hand facing forward. The equivalent toe configurations were used for the foot stimuli. Each pair of hands or feet subtended ~5° of visual angle. The apparatus consisted of an

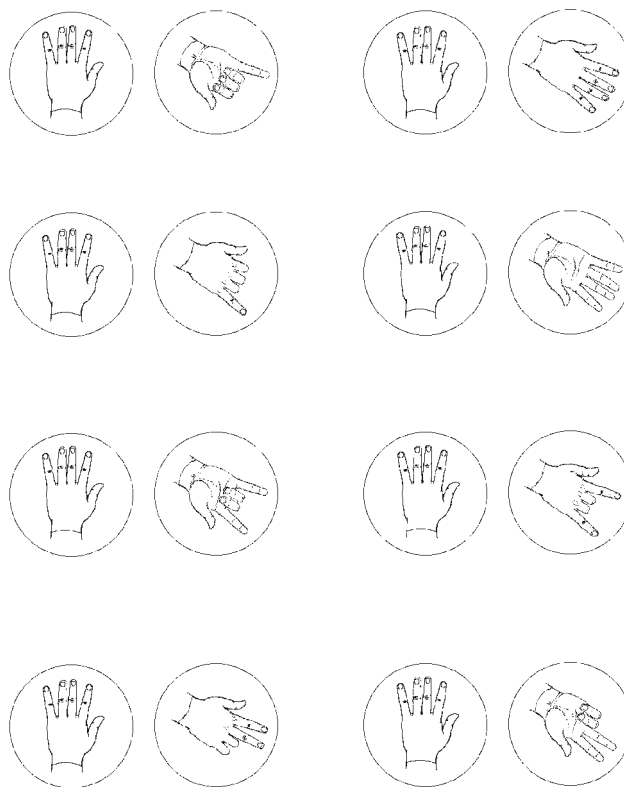


Figure 1. Drawings of hands used in the mental rotation task (illustrating here the 120° rotation). The same configurations were used for the drawings of feet.

Apple Macintosh® 6300 computer with a 14-in. Apple monitor (refresh rate 75 Hz). The experiment was conducted with SuperLab (version 1.71), which was also used to acquire voice onset RTs.

Procedure

The subjects were fitted with a tight-fitting Lycra swim cap. The head was kept still by means of a custom-made chin rest placed ~60 cm from the monitor. During real TMS, single pulses (delivered with the MagStim Super Rapid Magnetic Stimulator, The Magstim Company, Wales, UK) were delivered over the left motor cortex hand area. The stimulator delivers well-compensated biphasic pulses. Pulses were delivered with a small 8-shaped coil in which each wing measures 4.3 cm in diameter. The TMS device was externally triggered using a TTL output pulse from the computer that ran the task. A clocking board in the computer assured a temporal resolution of <16.3 ms for the delivery of this TTL pulse. The site of stimulation was the optimal scalp position over the left hemisphere for induction of motor-evoked potentials in the right thenar eminence. This optimal scalp position was defined following the guidelines of the International Federation for Clinical Neurophysiology. At this location the optimal orientation of the coil for activation of the target muscle was defined by assessing the amplitude of the motor evoked potentials at various angles of the coil handle relative to the mid-sagittal plane. For the duration of the study the coil orientation was then held constant. Stimulation intensity was set at 120% of the motor threshold for the target muscle. Motor threshold was determined for each subject independently according to the guidelines of the International Federation for Clinical Neurophysiology. The intensity of the pulse (120% of motor threshold) was determined in order to be as high as possible, thereby maximizing the chance of local disruption of neural function without producing blinks or excessive discomfort.

Because suprathreshold TMS of motor cortex elicits an overt movement, we needed a magnetic stimulation site that elicited a similar movement. Otherwise, the effect of TMS could be due to some indirect interference of the elicited movement of the hand on the mental rotation of hands, rather than to disruption of neural activity. This was achieved

by delivering magnetic stimulation with the same coil to the right flexor carpi radialis at the same relative intensity as the TMS. This peripheral nerve magnetic stimulation (PNMS) induced a hand movement similar to the one elicited by the suprathreshold TMS. For simplicity in the rest of the paper the term 'magnetic stimulation' (MS) will be used to refer to both TMS and PNMS.

The experiment began with written instructions on the computer screen, after which subjects could ask for verbal clarification from the investigator. Each trial began with a black fixation spot at the center of the computer screen on a white background (500 ms), followed by the pair of stimuli, which remained on the screen until a vocal response was given. Subjects were instructed first to rotate the hand (or foot, as appropriate) on the right to the vertical orientation and then to decide whether it was the same as the stimulus depicted on the left. They were to say the word 'same' or 'different' as quickly as possible after they had made a decision, but were asked to be as accurate as possible. Voice responses, rather than key responses, were employed to avoid potential interference with mental rotation processes (Wexler *et al.*, 1998; Wolschlagel and Wolschlagel, 1998).

Two intervals between the visual stimulus and the MS pulse were used: 400 and 650 ms. Pictures of hands and feet were tested in separate blocks; all the blocks with hands stimuli (a total of four, resulting from the combination of two ISIs by two MS types) were tested either before or after all of the blocks with feet. A practice session (16 trials) with the appropriate type of stimuli at orientations not used during the experimental trials preceded the blocks for each stimulus type. The order of MS type was counterbalanced across subjects, while the order of stimulus type and ISI was randomized. For each subject the same block order was used for the hand and foot stimuli.

Data and Statistical Analysis

RTs and error rates were measured. RT was defined as the time between appearance of the stimulus on the computer screen and onset of the verbal response by the subjects. Trials in which subjects did not speak loudly enough to trigger the voice box were eliminated before analysis (~2%, equally distributed across conditions). Trials in which RTs were 3 or more standard deviations above the mean for each cell, for each subject were also eliminated prior to the RT analysis (~2% of all trials). Only RTs from trials on which the correct response was made were analyzed. All trials were included in the calculation of error rates. The RTs and error rates were first analyzed in separate ANOVAs, conducted independently for the two ISI conditions. Each ANOVA had three factors: stimulus type (hands and feet), MS type (TMS and PNMS), and angle of rotation (20°, 60°, 100° and 140°). The use of voice onset RTs and of magnetic stimulation is likely to introduce noise in the data. Thus, in a second analysis we attempted to offset this additional noise by doubling the number of trials per cell. This was achieved by collapsing the 20° and 60° rotations (small rotation) and the 100° and 140° rotations (large rotations). Hence, in this second analysis there were only two levels in the rotation factor. The results of this analysis will not be reported as they are virtually identical to those in the main one, with all levels of rotation included.

Finally, to compare the effects across ISIs, we conducted an ANOVA using the MS effect as the dependent variable (difference scores: TMS minus PNMS) and ISI (400 ms versus 650 ms) and stimulus type (hands versus feet) as factors. In this analysis the rotation factor was collapsed. All main effects and interactions not reported were not significant, $P > 0.15$ in all cases.

Results

The RT results for all conditions are shown in Figure 2.

Blocks with MS at 400 ms ISI

For the RTs, only the main effect of angle of rotation was reliable [$F(3,27) = 11.16$, $P < 0.01$]. Linear contrasts performed on the four stimulus-by-MS-type combinations revealed that RTs increased linearly with angle of rotation (all $F_s > 20$, all $P_s < 0.001$), indicating that the subjects did in fact perform mental rotation to carry out the task (Kosslyn *et al.*, 1998). As is evident in Figure 2,

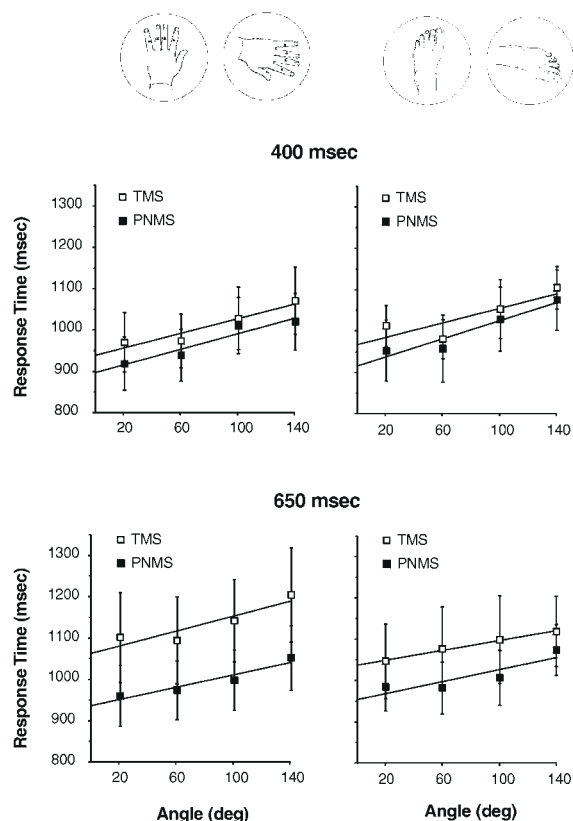


Figure 2. Average RTs for TMS (solid squares) and PNMS (empty squares), plotted as a function of angle of rotation. The top and bottom rows show the results obtained with an ISI of 400 and 650 ms respectively. The left and right columns show the results obtained with pictures of hands and feet respectively. Standard errors of the mean are also indicated.

a planned contrast showed no difference between PNMS in the hand versus foot conditions [$F(1,9) = 0.99$, $P > 0.3$], which suggests that the two tasks were equally difficult. There was no interaction between MS type and stimulus rotation [$F(3,27) = 0.771$, $P > 0.5$].

Error rates were 3.75%, 2.66%, 4.53% and 3.91% for the hand TMS, hand PNMS, foot TMS and foot PNMS conditions respectively. There were neither significant main effects nor interactions in these data. Planned linear contrasts performed on the four stimulus-by-MS-type combinations revealed no linear error rate increase with angle of rotation (all $F_s < 1.3$, all $P_s > 0.25$). In sum, TMS presented 400 ms after stimulus onset had no effects on mental rotation of hands and feet.

Blocks with MS at 650 ms ISI

Examination of the RTs when MS was delivered 650 ms after the stimuli revealed again a main effect of rotation [$F(3,27) = 8.23$, $P < 0.01$]. Linear contrasts performed on the four stimulus and MS type combinations revealed that RTs increased linearly with angle of rotation (all $F_s > 9$, all $P_s < 0.01$), which indicates that mental rotation was in fact used to perform the task. As illustrated in Figure 2, RTs were slower with TMS than PNMS [1111 versus 1004 ms; main effect of MS type: $F(1,9) = 5.41$, $P < 0.05$]. There was no interaction between MS type and rotation [$F(3,27) = 0.155$, $P > 0.8$]. As shown in Figure 3 the effect of MS type was larger for hands than for feet [1137 and 995 ms versus 1085 and 1012 ms respectively; interaction of MS type by stimulus type: $F(1,9) = 6.67$, $P < 0.05$]. Planned contrasts

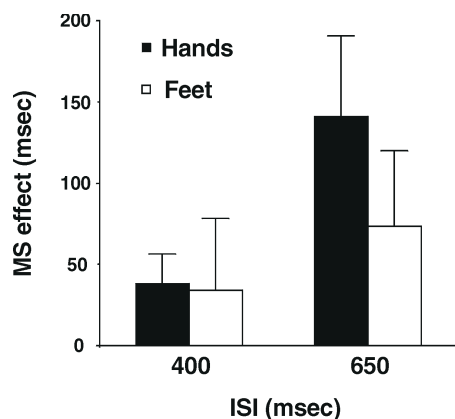


Figure 3. Average MS effect, defined as the difference between RTs in the TMS and PNMS conditions, plotted for all four stimulus-by-ISI conditions. Results are collapsed across angles of rotation.

revealed that stimulation type had a reliable effect on both hands and feet [$F(1,9) = 57.89$, $P < 0.001$ and $F(1,9) = 15.66$, $P < 0.01$ respectively]. A third planned contrast revealed no difference between PNMS in the hand and foot conditions [$F(1,9) = 0.76$, $P > 0.4$], suggesting that the two tasks were equally difficult.

Error rates were 4.25%, 4.15%, 3.95% and 4.15% for the hand TMS, hand PNMS, foot TMS and foot PNMS conditions respectively. There was only an interaction between MS type and rotation [$F(3,27) = 3.58$, $P = 0.041$]. Follow-up contrasts showed that the error rates were higher for TMS than PNMS, but only at 60° of rotation [$F(1,9) = 5.3$; $P = 0.03$, uncorrected]. Planned linear contrasts performed on the four stimulus-by-MS-type combinations revealed no linear error rates increase with angle of rotation (all F s < 1.3 , all P s > 0.25).

Comparison of MS effects across ISIs

We compared the MS effects across ISIs with a two-way ANOVA on the difference scores (TMS minus PNMS) using ISI and stimulus type as factors (Fig. 3). In this analysis the rotation factor was collapsed because it did not interact with stimulus type in the previous analyses. There was a main effect of ISI [$F(1,9) = 5.2$, $P < 0.05$], indicating that the MS effect was larger at 650 ms than at 400 ms. There was also an interaction of stimulus type and ISI [$F(1,9) = 5.3$; $P < 0.05$]. Follow-up contrasts showed that the MS effect was larger for hands than feet at 650 ms [$F(1,9) = 12.0$, $P < 0.01$] but not at 400 ms [$F(1,9) = 0.043$; $P > 0.5$].

Discussion

Three inferences can be drawn from the present results. First, the left primary motor cortex is involved in the mental rotation of pictures of hands. This finding is consistent with previous brain imaging results (Lang *et al.*, 1994; Porro *et al.*, 1996; Kosslyn *et al.*, 1998), and is also consistent with recent findings showing that corticospinal excitability is enhanced during motor imagery of movements, but only for those muscles that would be recruited were the overt movements executed (Fadiga *et al.*, 1999). As described in the introduction, only a subset of brain imaging studies have found evidence of primary motor cortex involvement in motor imagery. This variability could be due to the different stimuli and paradigms employed, or to the different imaging techniques used, or to both (Parsons and Fox, 1998).

Second, motor cortex involvement is stimulus specific, as

witnessed by the fact that disruption of neural activity in the hand area slowed mental rotation of pictures of hands more than that of feet. The selective role of the hand area in mental rotation of hands is unlikely to be due to differential task difficulty, given that there were no reliable differences between the RTs in the hands and feet PNMS conditions.

And third, left primary motor cortex is involved relatively late in the rotation process. In our study MS effects were obtained with stimulation at 650 ms but not at 400 ms after stimulus onset. Of course, the absence of a reliable MS effect at 400 ms could be due to low statistical power; however, the MS effect at 400 ms was reliably smaller than at 650 ms, indicating at least that the involvement of primary motor cortex in the rotation process is less pronounced at 400 than 650 ms. This finding is in general agreement with MEG data suggesting that during implicit movement of hands activity in frontal premotor cortices begins after 400 ms, following earlier activation in occipital and parietal cortices (Kawamichi *et al.*, 1998). Our findings, in combination with these earlier results, suggest that motor representations begin to be used in the mental rotation of pictures of hands between 400 and 650 ms after the process begins. These findings also suggest that prior to 400 ms the primary processes taking place are concerned largely with visuospatial encoding, presumably occurring in occipital and parietal regions.

It is important to note that single-pulse TMS did not affect the *speed* of mental rotation: there were no reliable interactions of MS type by angle of rotation. This is not surprising because the disruption produced by a single TMS pulse lasts only a few milliseconds, unlike the prolonged effects on cortical excitability produced by long trains of TMS pulses (Pascual-Leone *et al.*, 1997). This MS effect may reflect disruption of a process involved in the transformation between visual and motor representations taking place just before the rotation process; or it may reflect disruption of early stages of the rotation process itself. It has been suggested that at least some types of visual mental rotation are covert simulations of motor rotation in which people imagine what they would see if the simulated action were executed (Kosslyn, 1994). Frontoparietal loops (Rizzolatti *et al.*, 1998) could simulate the temporal unfolding of the rotation and its visual consequences using stored visuomotor correlations. A neural computational model of how these sequences of correlations might be learned and reactivated in multi-area systems was proposed by Zhang (Zhang, 1994).

In addition, at 650 ms there was a reliable effect of TMS not only for hands but also for feet. There are a number of potential explanations for this effect. First, TMS is more likely to induce a generalized disruption than PNMS if only because the coil is closer to the subject's ears and the generated noise may be more distracting. According to this account, the TMS effect for feet would not reflect disruption of mental rotation of feet *per se*. However, since we saw no disruption with TMS applied at 400 ms we feel that this is unlikely. Second, people may use the hand representation to rotate not only hands but to some extent also feet. Hands and feet are topologically very similar, but hands are much more familiar stimuli. Hence, people could actually map the picture of a foot onto the motor representation of the hand. Third, the TMS pulse to the hand area may have also affected neural activity in the foot area via corticocortical connections. However, this is unlikely because no mouth movements were observed, despite the proximity of its motor representation to that of the hand. In addition, studies of intracortical connectivity in primate motor cortex have failed to reveal connections

between upper and lower extremity representations (Huntley and Jones, 1991). Furthermore, the spatial selectivity of single-pulse TMS has been demonstrated in the visual system by Beckers and Zeki (Beckers and Zeki, 1995). They found that TMS stimulation over area V5 impaired motion perception but not color and shape perception. In contrast, TMS to V1 disrupted detection of visual stimuli without affecting motion perception. Areas V5 and V1 are interconnected, and thus, if the effects of TMS on a given area were due to transsynaptic effects, TMS to V1 should disrupt motion perception (by remotely affecting neural activity in V5), and TMS to V5 should disrupt visual stimulus detection (by remote effects onto V1). This was not the case. Note that the claim is not that activity does not spread to remote brain regions. Clearly, stimulation of a cortical area can have remote effects on other areas connected to it; if this was not the case it would not be possible to induce MEPs by stimulation of primary motor cortex. The crucial issue regarding spatial selectivity, however, is whether these remote effects can affect behavior. The study by Ilmoniemi and collaborators (Ilmoniemi *et al.*, 1997), for example, shows propagation of activation with stimulation at motor cortex. However, the behavioral relevance of this propagation was not examined. The study by Beckers and Zeki, on the other hand, shows directly that propagation of activity to remote areas is not associated with behavioral effects (Beckers and Zeki, 1995). Obviously the question that arises is why this might be the case. One possibility is that the remote activation of distributed cortical areas might be too weak or too distributed in time for a functional disruption. Probably, synchronization of the stimulation plays a crucial role for a given effect as does temporal summation.

From these data alone we cannot discount the possibility that stimulation anywhere in primary motor cortex (i.e. not only in the hand area) would disrupt mental rotation of hands more than that of feet. However, this seems unlikely given the resolving power of the TMS pulse and the well-documented localization of function within this area (Huntley and Jones, 1991).

Finally, it is important to explicitly address the issue of the control condition employed in this study. Any control condition (peripheral or brain) is problematic in one way or another. With a cognitive task such as mental rotation it is not obvious which brain areas are clearly not participating in the task. Occipital, temporal, parietal and frontal cortical regions have all been shown to be, or claimed to be, involved in mental rotation. Thus, especially in the absence of same-subject MRIs and/or functional data, it is problematic to select a brain area that can function as a 'pure' control. Even if it were possible to find such a control area, it would still be the case that its stimulation does not evoke a hand movement, as occurs when primary motor cortex is stimulated (this is why we chose a peripheral stimulation site that elicited the same hand movement). Because of these potential problems we went one step further and introduced an additional foot rotation control condition. This is as close as we could come to an ideal control condition because the *same* brain area is stimulated and only the stimulus is varied. The absence of a difference between the foot and hand rotation conditions during PNMS demonstrates that the two stimuli are equally difficult to rotate. The larger MS effect for hand than foot rotation at 650 ms shows that TMS affects hand rotation more than foot rotation. By using the foot condition as control we subtract out all the potential artifacts that are inherent in using stimulation of a different area as control condition.

In summary, the present results strongly support the claim that the hand area in primary motor cortex has a causal role in

the mental rotation of hands. On average, the recruitment of the motor cortex occurs between 400 and 650 ms, probably after earlier recruitment of occipital and parietal brain regions.

Notes

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