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RESEARCH NOTE

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Mirror, mirror on the wall: viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability

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Abstract Primary motor cortex (M1) excitability is modulated by both ipsilateral limb movement and passive observation of movement of the contralateral limb. An interaction of these effects within M1 may account for recent research suggesting improved functional recovery of the impaired arm following stroke by viewing a mirror reflection of movements of the unimpaired arm superimposed over the (unseen) impaired arm. This hypothesis was tested in the present study using single-pulse transcranial magnetic stimulation (TMS) in eight neurologically healthy subjects. Excitability of M1 ipsilateral to a phasic, unilateral hand movement was measured while subjects performed paced (1 Hz), unilateral index finger-thumb opposition movements. Motor evoked potentials (MEPs) were obtained from the inactive first dorsal interosseous (FDI) in each of four viewing conditions: Active (viewing the active hand), Central (viewing a mark positioned between hands), Inactive (viewing the inactive hand) and Mirror (viewing a mirror-reflection of the active hand in a mirror oriented in the mid-sagittal plane) and with both hands at rest (Rest). MEPs were significantly enhanced during ipsilateral hand movement compared with the Rest condition ($P < 0.05$). Largest MEPs were obtained in the Mirror condition, and this was significant compared with both the Inactive and Central viewing conditions ($P < 0.05$). There was no difference between the dominant and non-dominant hand. Excitability of M1 ipsilateral to a unilateral hand movement is facilitated by viewing a mirror reflection of the moving hand. This finding provides neurophysiological evidence supporting the application of mirror therapy in stroke rehabilitation.

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Introduction

Voluntary unilateral arm/hand movement induces excitability changes in both the contralateral and ipsilateral primary motor cortex (M1) (Liepert et al 2001; Muellbacher et al 2000). Because modulation of M1 excitability is an important neural mechanism involved in the induction of neuroplasticity (Bütefisch et al 2000; Muellbacher et al 2001, 2002), incorporating motor tasks that induce M1 excitability changes into movement therapies may improve their effectiveness in promoting functional recovery of the impaired side following mono-hemispheric stroke. The finding that arm and hand movement alters excitability of *ipsilateral* M1 is of interest, as this suggests that movements of the unimpaired limb might benefit functional recovery of the impaired limb. Results from studies of bilateral movement therapy, in which stroke patients perform movements of both the impaired and unimpaired limbs simultaneously, are consistent with this suggestion (Mudie and Matyas 1996; Whitall et al 2000).

Another therapeutic intervention that capitalises on moving the unimpaired limb, and one which is the focus of the present paper, is mirror therapy (Altschuler et al 1999; Sathian et al 2000; Stevens and Stoykov 2003). In mirror therapy, originally used to treat "phantom limb" pain in amputees (Ramachandran and Rogers-Ramachandran 1996), stroke patients perform movements of the unimpaired limb while watching its mirror reflection superimposed over the (unseen) impaired limb, thus creating a visual illusion of enhanced movement capability of the impaired limb. Although these studies involved a relatively small number of patients, the findings suggest that mirror therapy may be a promising approach for treating stroke-induced

hemiparesis (Altschuler et al 1999; Sathian et al 2000; Stevens and Stoykov 2003). At present, the neural basis of the putative therapeutic effect is unknown. However, it may involve an interaction within the impaired M1 between the mechanisms mediating excitability changes associated with ipsilateral (unimpaired) limb movement and excitability changes associated with movement observation (Aziz-Zadeh et al 2002; Strafella and Paus 2000).

Several studies report that passive movement observation, in the absence of overt movement of either limb, facilitates M1 excitability specifically for muscles engaged in the observed action (Aziz-Zadeh et al 2002; Maeda et al 2002; Strafella and Paus 2000). This situation is reproduced when viewing a mid-sagittal mirror-reflection of one's own hand. The proposal that seeing a mirror reflection of the moving ipsilateral limb (mirror viewing) has a differential effect on M1 excitability than ipsilateral limb movement alone (no mirror reflection) is supported by studies of phantom limb patients. Ramachandran and Rogers-Ramachandran (1996) reported that four of five patients who experienced "clenching spasms" of their phantom hand were unable to relax the phantom in the absence of the mirror image. A similar finding of improved control of the phantom limb in the presence of a mirror reflection of the intact limb was also reported by Brodie et al (2003).

If it is correct that mirror viewing affects M1 excitability ipsilateral to the moving limb, this may be visible through changes in the size of motor evoked potentials (MEPs) produced by transcranial magnetic stimulation (TMS). To date, the effect of movement observation on M1 excitability has only been assessed while subjects were completely passive (when both hands are relaxed). Using a group of neurologically healthy subjects, we show for the first time that mirror viewing leads to an additional facilitation of M1 beyond that produced by ipsilateral hand movement alone.

Methods

Eight (four male, four female, 39.6 ± 14.5 years) neurologically healthy subjects from the University of Tasmania community participated in the study. Six subjects were self-declared right hand dominant and two were left hand dominant. All procedures were conducted in accordance with the 1964 Declaration of Helsinki and approved by the Ethics Committee of the University of Tasmania. All subjects gave informed written consent prior to participation.

Transcranial magnetic stimulation

Transcranial magnetic stimulation was performed using a single Magstim 200 stimulator (Magstim, Gwyneth, Dyfed) connected to a flat circular coil (9 cm diameter). In separate trials, MEPs were recorded from the first dorsal interosseous (FDI) muscles of the dominant and non-dominant hands using surface Ag/AgCl electrodes. One electrode was placed over the belly of the muscle and the other on the metacarpophalangeal joint. The reference electrode was placed over the right lateral malleolus. EMG signals were amplified (1,000×) and band-pass filtered (10–2,500 Hz) prior to sampling (2,000 Hz) using a 12-bit AD system and stored on computer hard-disk for analysis offline. The TMS coil was positioned tangential to the scalp and centred over on the vertex, with the A-side up to evoke MEPs in right-side muscles and the B-side up to evoke MEPs in left-side muscles. TMS intensity was adjusted to yield consistent MEPs with a peak amplitude of approximately 0.5 mV in the target FDI when both hands were at rest. Mean TMS intensities were 56.6% (± 7.3 SEM) and 54.3% (± 7.0 SEM) for the left and right hand respectively. This difference was not statistically significant ($t_7 = 0.7$, $P = 0.489$).

Procedure

Subjects were seated with their hands in neutral positions and the ulnar sides of the hands and forearms resting on table surfaces directly in front of them. The motor task involved a simple, unilateral index finger-thumb opposition movement consisting of both a phasic and tonic component. A 1 Hz auditory metronome (1,000 Hz tone, 400 ms duration) was used to pace the movement. One complete open-close cycle was performed on each beat of the metronome. Subjects were instructed to synchronise the closing phase of the movement with the onset of the metronome beat and to tonically maintain the finger and thumb in opposition for the duration of the tone (400 ms) using moderate force (approximately 20% maximum). On the opening phase, subjects were instructed to open the finger and thumb to near maximum aperture. Each trial lasted 60 s (60 movement cycles), and single-pulse TMS was delivered on every fifth movement (0.2 Hz), yielding eleven MEPs. The TMS pulse was delivered 100 ms after the onset of the metronome beat (during the tonic phase). Subjects performed two blocks of five trials, one with the dominant and one with the non-dominant hand. On four trials, the motor task was performed under different viewing conditions: Active, Central, Inactive and Mirror (see Fig. 1). In the Active and Inactive viewing conditions, subjects visually fixated one hand (active or inactive) while vision of the unattended hand was prevented by covering it with a wooden box. In the Central viewing condition, subjects visually fixated a mark (square piece of tape) midway between the hands. In the Mirror viewing condition, subjects watched a mirror reflection of the active hand, with the inactive hand positioned (unseen) behind the mirror such that the reflected hand appeared superimposed over top of it. On the fifth trial, MEPs were recorded while both hands were relaxed (Rest) and

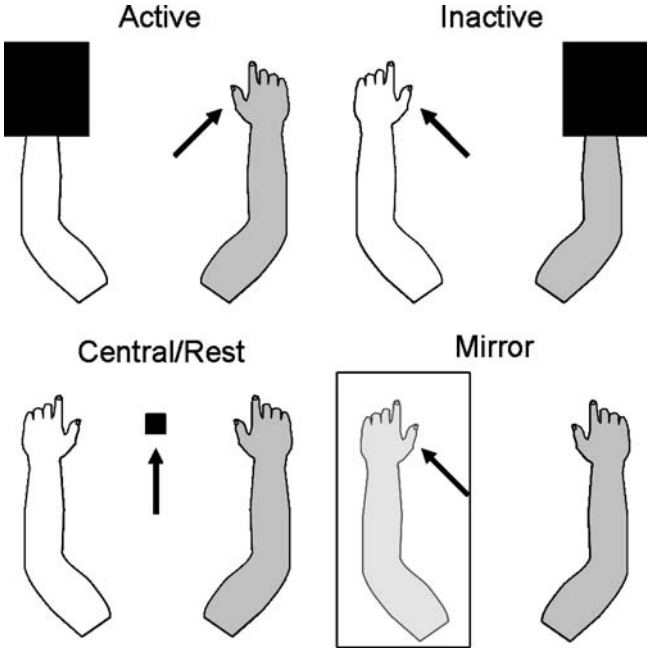

Fig. 1 Schematic illustration of the different viewing conditions when the right hand is the active hand (*gray*). MEPs were measured from the inactive (*white*) left hand. The *arrow* in each condition indicates where subjects were instructed to look

subjects visually fixating the central mark. This condition allowed us to determine the effect of the movement task itself on M1 excitability. Trials were presented in random order within each block, and the hand performing the movement task first was randomised across subjects. For all trials, EMG activity of the target (inactive) FDI was monitored online to ensure complete relaxation was maintained. Individual MEPs were excluded from the analysis if the mean rectified EMG activity in the target FDI during the 50 ms immediately preceding the TMS pulse exceeded 25 μV. Subjects had little difficulty maintaining relaxation of the target FDI and only 1% of trials were rejected for this reason. Subjects were allowed a brief rest period following each trial to minimise possible fatigue effects.

Data analysis

The peak amplitude of individual rectified MEPs was measured in each viewing condition. MEPs are known for their large intra- and inter-individual variation (Rossini and Rossi 1998). To minimize the influence of intra-individual variation, the median MEP amplitude (rather than the mean) was used as the measure of central tendency. Because our major interest was the effect of changes in the viewing condition on M1 excitability *during* ipsilateral hand movement, the influence of inter-individual MEP variation was minimised by normalising MEPs in all conditions to the Active viewing condition. This condition was selected because visual attention is normally directed to the active hand during unilateral hand movements and the Active condition was therefore the closest match to natural conditions. Because this procedure results in an MEP amplitude of 1 in the Active viewing condition for all subjects, statistical analyses were conducted using the non-parametric Friedman's two-way analysis of variance. Contingent upon a significant χ^2 value, post hoc comparisons were conducted using Wilcoxon signed-ranks tests. As MEP size in the inactive hand is influenced by the strength of contraction of the active hand (Liepert et al 2001; Muellbacher et al 2000), we also analysed peak EMG activity of the active hand during the 400 ms preceding each TMS pulse. Peak EMG was quantified as the maximum mean EMG level in the rectified trace within a moving 20 ms window. The median value of peak EMG was analysed using repeated measures ANOVA with hand (left, right) and viewing condition (Central, Active, Inactive, Mirror) as factors. Significance for all tests was set at $P < 0.05$.

Results

Peak EMG did not significantly differ across the four viewing conditions (Active = 520.7 ± 71.8 μV; Central = 558.2 ± 80.6 μV; Inactive = 520.4 ± 82.0 μV; Mirror = 487.8 ± 77.2 μV, $F_{(3,21)} = 2.0$, $P = 0.152$). Neither the main effect of hand ($F_{(1,7)} = 2.2$, $P = 0.182$) nor the hand by viewing condition interaction ($F_{(3,21)} = 1.6$, $P = 0.230$) were significant, indicating that subjects performed the motor task similarly across viewing conditions. Based on these findings it is unlikely that the following effects on MEP size could be accounted for by differences in task performance.

The analysis of MEP data was carried out in two steps. First, to determine whether there was an interaction between viewing condition and hand, the arithmetic differences between the normalised MEPs of the two hands were analysed using Friedman's non-parametric ANOVA. This did not reveal any significant differences ($\chi^2_4 = 5.1$, $P = 0.277$), indicating no hand asymmetry across the five conditions. The data were therefore collapsed across hand prior to analysing the effect of viewing condition. Viewing condition had a significant effect on MEP size ($\chi^2_4 = 18.9$, $P = 0.001$), and this is summarised in Fig. 2. Post hoc comparisons (Wilcoxon) revealed that MEPs in all four active conditions were significantly enhanced relative to the Rest condition (44.2 ± 6.3%) (all $P < 0.02$), indicating the motor task had an overall facilitatory effect on ipsilateral M1 excitability. Among the four active conditions, MEPs were significantly larger in the Mirror condition (121.7 ± 8.7%) than both the Central (93.6 ± 4.5%, $P = 0.025$) and Inactive (95.3 ± 8.7%, $P = 0.036$) conditions, while the difference between the Mirror and Active viewing conditions (100%) showed a trend toward significance ($P = 0.069$). No other differences were significant.

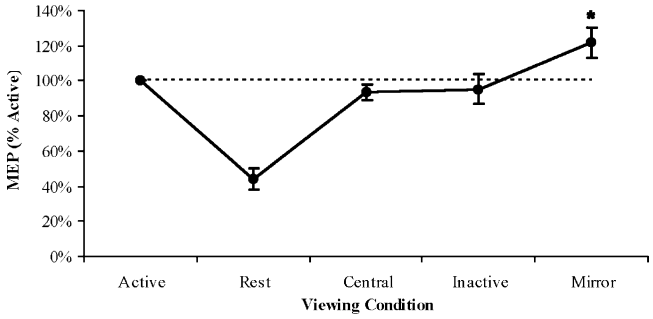

Fig. 2 Normalised MEP amplitude in each condition collapsed across the dominant and non-dominant hand. MEPs were significantly facilitated in all conditions relative to Rest ($P < 0.02$). MEPs in the Mirror condition were significantly facilitated compared with both the Inactive and Central conditions (*asterisks* denote $P < 0.05$)

Discussion

The present study tested whether excitability of M1 ipsilateral to a phasic, unilateral hand movement is modulated by viewing a mirror reflection of the active hand superimposed upon the (unseen) inactive hand. The major finding was that mirror viewing enhanced facilitation of ipsilateral M1. In addition, this effect did not differ between the dominant and non-dominant hand. The largest differences were found between the Mirror viewing condition and those conditions where movement was not directly observed (Central and Inactive). By contrast, the difference between the Mirror and Active viewing conditions, in which subjects viewed the active hand directly, just failed to reach a conventional level of significance. This may indicate a small generalised facilitation of ipsilateral M1, regardless of whether ipsilateral or contralateral hand movement is observed. This suggestion is partially supported by a study of movement observation in passive subjects, which found that, at least for the left hemisphere, MEP facilitation induced by movement observation did not differ significantly, regardless of whether subjects observed movement of the contralateral or ipsilateral hand (Aziz-Zadeh et al 2002).

Ipsilateral M1 excitability is known to increase with increasing contraction strength (Liepert et al 2001; Muellbacher et al 2000). A possible explanation for the present findings, therefore, is that the greater MEP amplitude in the mirror viewing condition resulted from subjects performing the motor task more forcefully. Although we did not obtain a direct measure of contraction strength, the analysis of pre-stimulus peak EMG suggests that this explanation is unlikely: peak EMG amplitude did not differ significantly among the four viewing conditions. In fact, peak EMG activity was lowest overall (though not significantly) in the Mirror viewing condition.

Possible mechanism

Modulation of MEP amplitude assessed with single-pulse TMS can reflect changes in excitability of both cortical and subcortical (in other words, spinal) neural mechanisms. It is therefore not possible from the current study to conclusively identify the level at which facilitation occured. However, converging evidence suggests the effect is likely of cortical origin. First, while subcortical excitability changes can influence MEP amplitudes when high force (>50% maximum) ipsilateral contractions are performed (Stedman et al 1998), this influence is absent during low force contractions (Liepert et al 2001; Stedman et al 1998). As low force contractions (~20% maximum) were used in the present study, and EMG activity in the active hand did not vary across conditions, it is unlikely that spinal mechanisms played a significant role. Second, motor imagery, which may involve similar mechanisms to movement observation (Maeda et al 2002), facilitates MEPs but not spinal excitability (Facchini et al 2002). Finally, Strafella and Paus (2000) found that movement observation is associated with effector specific reduction of excitability of intracortical inhibitory (ICI) circuits, pointing to a cortical locus. Based on the preceding evidence, we suggest that the Mirror condition in the present study may have lead to reduced ICI, resulting in an increase of MEP amplitude. If correct, this could have important implications for rehabilitation given the role of reduced ICI in the induction of neuroplasticity (Bütefisch et al 2000). As ICI was not assessed in the present study, however, this conclusion remains speculative.

In healthy subjects, executing a movement while simultaneously observing an incongruous movement interferes with performance of the executed movement (Kilner et al 2003). This interference is thought to reflect an overlap of the neural circuits activated by observation of the incongruous movement and those involved in movement execution. Since the unimpaired arm typically makes smoother movements than the impaired arm, a similar effect may arise in stroke patients during mirror therapy. However, in this case, the effect may ultimately prove beneficial, since any overlap would occur in circuits best suited to performing the smooth movement observed in the mirror. Such an overlap, together with the combined effects of mirror viewing and the ipsilateral limb movement on M1 excitability found in the present study, could optimise practice-induced neuroplasticity within the affected M1 of stroke patients, and as such be the mechanism responsible for the putative therapeutic benefit of mirror therapy reported by others (Altschuler et al 1999; Sathian et al 2000; Stevens and Stoykov 2003).

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