



Investigation of the transcallosal ventral premotor cortex connection in humans using transcranial magnetic stimulation

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Background: The premotor cortex plays a role in the planning of movement. Previous transcranial magnetic stimulation (TMS) studies have shown ipsilateral premotor-to-motor inhibition in healthy subjects at rest. Moreover, this premotor-to-motor inhibition has been found to be modulated during preparation for movement, such as precision grip and whole hand grasp. Cooperation between the bilateral ventral premotor cortices may play a functional role. We aimed to investigate the influence of the contralateral on the ipsilateral ventral premotor cortex.

Methods: Fourteen right-handed healthy subjects (six women and eight men; mean age, 37 years; standard deviation, 14 years) completed the study. We used a three single-pulse TMS paradigm (preconditioning, conditioning and test pulse) to sequentially stimulate the right ventral premotor cortex, left ventral premotor cortex and left primary motor cortex.

Results: We found that in healthy subjects at rest, stimulating the contralateral ventral premotor cortex resulted in reversal of the resting premotor-to-motor inhibition.

Conclusions: Our results suggest that the contralateral ventral premotor cortex exerts an inhibitory influence on the ipsilateral ventral premotor cortex, which may be a component of bi-hemispheric control of manual tasks. This is the first study to evaluate the functional connectivity between the bilateral ventral premotor cortices.

Key words: Premotor; Ventral; Transcallosal; Inhibition; Connectivity; Transcranial magnetic stimulation

INTRODUCTION

The interactions involving the primary motor cortex (M1) and other brain regions, notably the premotor,^{1,2} supplementary motor³ and posterior parietal⁴ cortices are critical in planning movement. Connectivity of the M1 and other regions has been investigated in studies using various neurophysiological modalities, including transcranial magnetic stimulation (TMS) and functional imaging. TMS is a noninvasive brain stimulation technique that passes a brief electric current through a magnetic coil.⁵ This results in excitation or inhibition of a focal brain region located below the coil. TMS can therefore be used to map brain function and probe the excitability and connectivity of different regions. Previous TMS studies performed largely on healthy human subjects have reported influences on M1 coming from other regions, including ventral (PMv) and dorsal (PMd) premotor cortices, bilateral posterior parietal cortices, cerebellum and contralateral M1.^{1,2,4,6-10}

The premotor cortex has been an area of interest particularly with respect to motor control. It has been demonstrated in several paired-pulse TMS paradigms that in healthy human subjects at rest, there is an ipsilateral premotor-to-motor inhibition when the PMv is stimulated using lower intensities.^{2,11} This resting inhibition has been observed in both ventral and dorsal premotor cortices, and further shown to be involved in specific types of grasp. For example, a repetitive transcranial magnetic stimulation (rTMS) study found the PMv to be specifically involved in precision grip, in contrast to the PMd, which was shown to be involved in whole hand grasp.¹² Lesioning of either PMv resulted in a larger variability of finger positioning, suggesting that these areas contribute to the visuomotor transformations necessary for efficient grasping and that their communication might be important. The role of the PMv in precision grip was further corroborated by a paired-pulse TMS study, with findings of reversal of the resting premotor-to-motor inhibition during whole hand grasp, turning into facilitation with precision grip.² The PMv is therefore also thought to be involved in performance of different types of grasp.

Transcallosal connections between bilateral ventral and dorsal premotor cortices have previously been verified based on anatomical data obtained from macaque monkeys.^{13,14} More recent work using functional magnetic res-

onance imaging (fMRI) to study the connectivity between the bilateral premotor cortices during grasp has confirmed bilateral involvement of these areas during unilateral grasp execution.¹⁵ Interhemispheric inhibition between dorsal premotor and primary motor cortices has been observed during preparation of only unimanual movements.¹⁶ Furthermore, in patients with moderate-to-severe chronic stroke, stimulation of the premotor cortex was found to enhance interhemispheric functional connectivity in association with recovery in more impaired individuals.¹⁷ Functional connectivity-based neurofeedback has been proposed as a tool for motor recovery in disorders relevant to impaired interhemispheric connectivity such as stroke.¹⁸

To date, functional connectivity of the bilateral ventral premotor cortices using TMS has not been reported. Thus, little is known about the physiology of these two regions. In the current study, we aimed to investigate the transcallosal ventral premotor connection in healthy human subjects, by using a three single-pulse TMS paradigm to sequentially stimulate the right PMv, left PMv and left M1.

MATERIALS AND METHODS

Subjects

Eighteen healthy volunteers participated in this exploratory study. Four subjects were excluded from the study due to spatial constraints on the head that did not allow for proper ipsilateral PMv and M1 coil placement. Fourteen right-handed subjects (six women and eight men; ages, 24-69 years; mean age, 37 years; standard deviation, 14 years) completed the study, conducted in a single session. Subjects gave written informed consent prior to all experimental procedures, approved by the Institutional Review Board of the National Institutes of Health (NIH). Experimental procedures were performed in accordance with the Declaration of Helsinki and the NIH guidelines.

Experimental procedures

Electromyography (EMG)

Subjects sat relaxed in a chair, with both hands resting on a pillow placed on the lap. The ground electrode was placed over the dorsum of the right hand. EMG recordings were ob-

tained from the right first dorsal interosseous (FDI) muscle, using surface Ag-AgCl electrodes. The EMG signal was amplified using an EMG machine (Nicolet Biomedical, Madison, WI, USA), digitized at 5,000 Hz, bandpass-filtered at 10-2,000 Hz and recorded by a computer using Signal software (Cambridge Electronic Design, Cambridge, UK).

TMS

Three high-power Magstim 200 monophasic stimulators

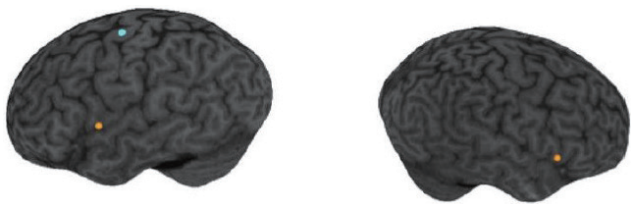
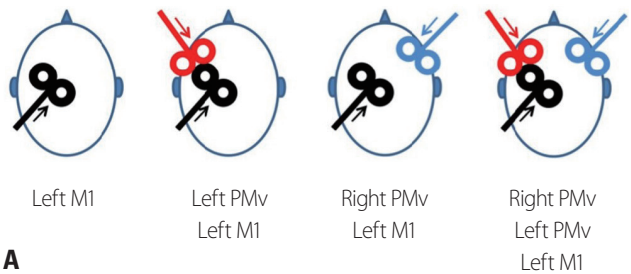


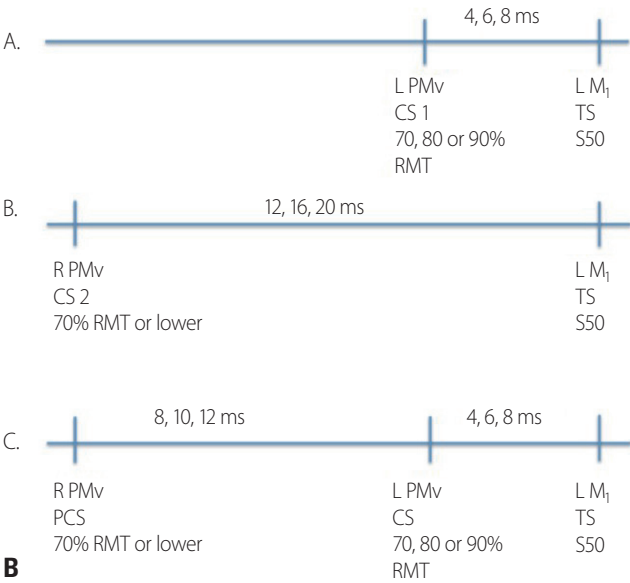
Fig. 1. Sites of TMS. Example of the location of stimulated areas (left PMv, left M1, and right PMv) in one subject, as shown in Brainsight (Rogue Research, Inc., Cardiff, UK). The orange dots indicate left and right PMv, and the blue dot indicates L PMv. TMS, transcranial magnetic stimulation; PMv, ventral premotor cortex; M1, primary motor cortex; L PMv, left ventral premotor cortex.



A

(Magstim Co., Whitland, UK) were connected to three figure-of-8, branding-iron style coils with an external loop diameter of 40 mm. The left and right PMv were identified using Brainsight (Rogue Research, Inc., Cardiff, UK), a neuro-navigation system that allows for specific target selection based on each subject's anatomical brain MRI (Fig. 1). The caudal portions of the pars opercularis of the inferior frontal gyrus² were identified as the areas to be stimulated for bilateral PMv. The mean montreal neurological institute coordinates of the left and right PMv areas stimulated were (x, y, z; mean \pm standard error of the mean in mm) -52.84 ± 3.62 ; 12.16 ± 8.42 ; 7.24 ± 4.63 ; and 54.66 ± 3.82 ; 12.94 ± 8.58 ; 9.80 ± 4.74 ; respectively, corresponding to the left and right inferior frontal gyrus within Brodmann area 44 on the Talairach atlas. Neuronavigation was used to monitor the coil location on the left and right PMv during the entire experiment in order to ensure consistent coil placement.

A TMS coil was placed tangentially on the surface of the head over the hand area of the left M1 to induce a posterior-to-anterior current. The motor hotspot was then determined, based on the motor evoked potential (MEP)



B

Fig. 2. Experimental conditions. (A) Schematic illustration of the coil positions on left PMv-left M1, right PMv-left M1 and right PMv-left PMv-left M1. The black coil illustrates the coil placed on the left M1. The red coil illustrates the coil placed on the left PMv. The blue coil illustrates the coil placed on the right PMv. (B) Experiment 1: conditioning of the left PMv prior to L M1 stimulation. Experiment 2: conditioning of the right PMv prior to L M1 stimulation. Experiment 3: sequential stimulation of the R PMv, L PMv and L M1. Interstimulus intervals are noted above, and stimulation intensities are noted below the respective brain regions. M1, primary motor cortex; PMv, ventral premotor cortex; L PMv, left ventral premotor cortex; L M1, left primary motor cortex; CS, conditioning stimulus; TS, test stimulus; RMT, resting motor threshold; R PMv, right ventral premotor cortex; PCS, preconditioning stimulus.

evoked in the right FDI muscle. Estimates of the resting motor threshold (RMT) and S50 (the stimulation intensity that produces an MEP that is 50% of the subject's maximal MEP), were obtained using a recruitment curve method that randomly delivered TMS pulses on the motor hotspot ranging from 5% to 100% intensity with 5% spacing. The left M1 was stimulated at the intensity of S50 in all experiments, as this is generally considered to be an intensity where the subject's corticospinal tract is most susceptible to modulatory influences and therefore likely results in a similar percentage activation of the motor neuron pool across all subjects. Experiments were conducted using the following three steps (Fig. 2).

In experiment 1, we aimed to reproduce the resting premotor-to-motor inhibition in order to functionally localize the left PMv, as previous studies have previously demonstrated in healthy human subjects at rest.^{2,11} The left PMv was stimulated using 90% RMT intensity, using anterior-to-posterior induced current, prior to stimulating the left M1. The interstimulus intervals (ISI) were set at 4, 6, and 8 ms, based on the results of these previous studies. This step was repeated using 80% RMT intensity, when there was no inhibition seen using 90% RMT intensity, and additionally at 70% RMT intensity if needed. Twenty trials were performed for each condition, with a 5-second inter-trial interval, resulting in 80 randomized pulses for each condition, including the test stimulus alone to serve as a control.

In experiment 2, we aimed to determine a stimulation intensity that would not directly influence the left M1, but potentially influence only the left PMv, as the transcallosal ventral premotor connection (right PMv-left PMv) was what we intended to study. The right PMv was stimulated using a conditioning intensity of 70% RMT prior to stimulation of the left M1. The ISIs were set as 12, 16, and 20 ms, reflecting the sum of the ISIs from the right PMv to left PMv (8, 10, and 12 ms, which will be used in the three single-pulse experiment), and left PMv to left M1 (4, 6, and 8 ms). The ISIs between bilateral PMv was determined based on the ISIs reported in previous interhemispheric inhibition (IHI) TMS studies.⁸ The data were then analyzed to ensure that the 70% RMT intensity stimulation had no direct effect (determined as <20% change of the test MEP amplitude) on the left M1. If it did, then we repeated this step with 60% RMT intensity, and so forth, until a conditioning intensity having no effect on the

left M1 was determined. A total of 80 pulses were delivered randomly for each session.

Experiment 3 was the main triple-coil experiment, which used three single pulses to sequentially stimulate the right PMv, left PMv, and left M1. The right PMv was stimulated using the conditioning intensity that was established in experiment 2. The left PMv was stimulated using the conditioning intensity established in experiment 1. The ISIs between the right and left PMv were set at 8, 10, and 12 ms. ISIs between the right and left PMv, and the left PMv and M1 respectively, were set as 8 ms, 4 ms; 8 ms, 6 ms; 8 ms, 8 ms; 10 ms, 6 ms; 12 ms, 4 ms; 12 ms, 6 ms; and 12 ms, 8 ms. These seven conditions and the test condition were presented randomly and a total of 160 pulses were administered.

Statistical analysis

The MEP amplitude measurements in millivolts were collected for each of the 20 trials and 16 conditions in all 14 subjects. The mean MEP amplitudes of the 20 trials were calculated for each subject at each condition. Natural log transformation was applied to the mean MEP amplitudes since its distribution was skewed, with a long right tail. The log-transformed mean was used as a response variable in the three experiments. For each experiment, a repeated-measures analysis of variance (RM-ANOVA) with compound symmetry as a covariance structure was performed to examine the effect of condition on the MEP amplitudes (the response variable). The condition had four levels in experiment 1 (test, 4, 6, and 8 ms) and experiment 2 (test, 12, 16, and 20 ms), and seven, eight levels (test; 8 ms, 4 ms; 8 ms, 6 ms; 8 ms, 8 ms; 10 ms, 6 ms; 12 ms, 4 ms; 12 ms, 6 ms; and 12 ms, 8 ms) in experiment 3. For each experiment, the Dunnett-Hsu method with the test condition as a control was used to adjust for the multiple comparisons in *post-hoc* analysis. The significance level of $\alpha = 0.017$ ($0.05/3$) was used to account for the three experiments. All the statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

The mean MEP amplitude evoked by stimulating M1 at S50 intensity (mean, 58%; standard deviation, 11.4%) was 2.0 mV,

with a standard deviation of 1.2 mV. The mean RMT was 45% with a standard deviation of 8.4%.

In experiment 1, we aimed to reproduce the resting pre-motor-to-motor inhibition in our subjects. Inhibition was seen at all ISIs (4, 6, and 8 ms), ($F(3, 39) = 10.1$; $p < 0.001$), maximal at 6 ms, as shown in Fig. 3A. The conditioning intensities used in this experiment were 90% RMT in 11 subjects and 80% RMT in two subjects, consistent with the conditioning intensities reported in prior studies. In one subject, premotor-to-motor inhibition was achieved using 70% RMT conditioning intensity. Multiple comparison with Dunnett-Hsu's method indicated that the mean MEP amplitudes of 4 ms, 6 ms, and 8 ms were significantly different from that of the test condition ($p < 0.005$), indicating that premotor-to-motor inhibition was present at all ISIs.

In experiment 2, there was no difference between the conditioned MEPs and the test pulse at all ISIs (12, 16, and 20 ms), confirming the absence of a direct effect of the contralateral PMv conditioning on M1 ($F(3, 39) = 1.1$; $p = 0.34$); (Fig. 3B). Therefore, we appropriately established a stimulation intensity that did not directly influence the left M1, but only influenced the left PMv. This step was required in order to be able to study the transcallosal ventral premotor connection. Stimulation intensities used to condition the contralateral PMv varied among subjects; 70% RMT was used in 12 subjects, 60% RMT in one subject, and 40% RMT in one subject.

In experiment 3, the main triple-coil experiment, there was no difference across all conditions ($F(7, 91) = 1.17$; $p = 0.33$), suggesting that preconditioning of the contralateral PMv

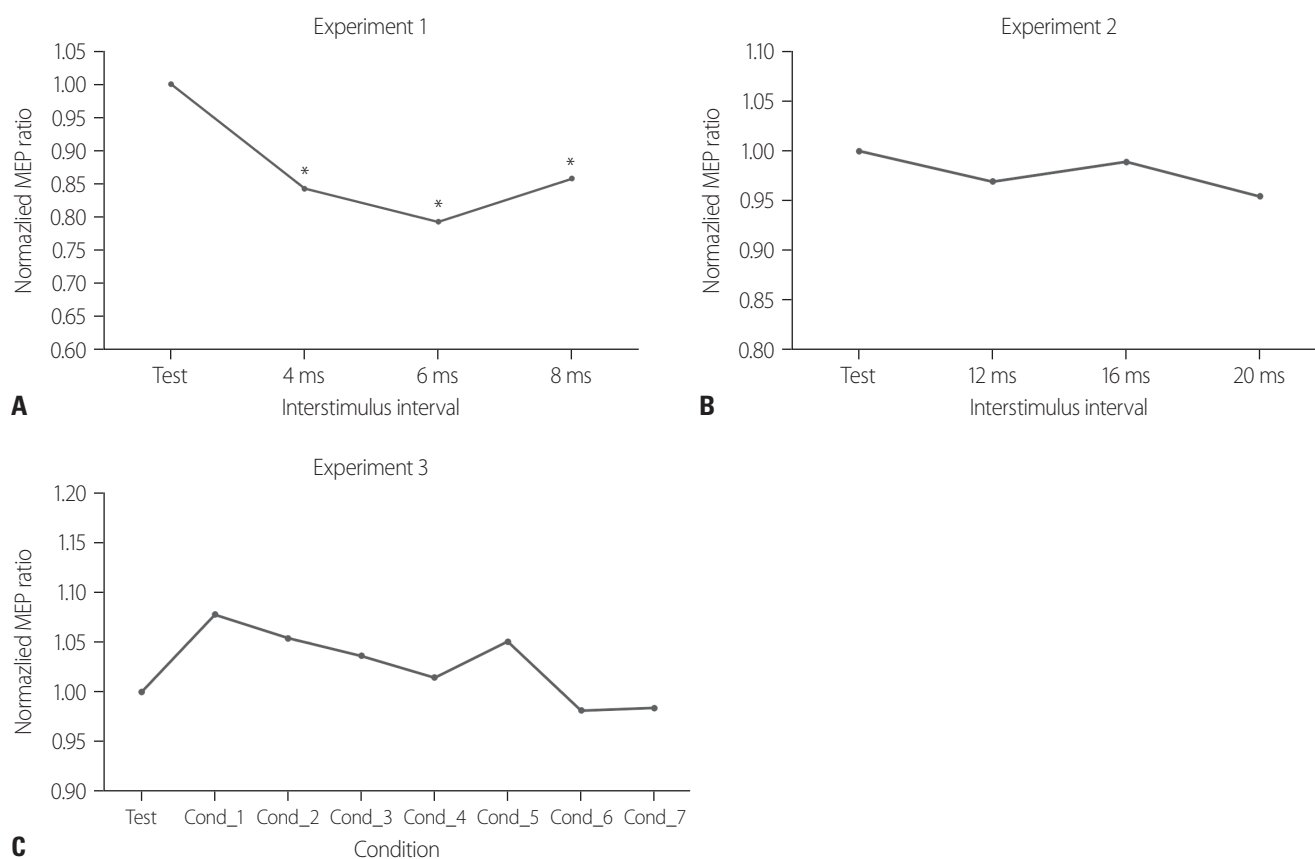


Fig. 3. Results of experiments 1, 2, and 3. (A) Ventral premotor-to-motor inhibition seen with paired-pulse TMS. Inhibition was seen with conditioning of PMv prior to M1 stimulation at all ISIs (4, 6, and 8 ms), with maximal inhibition seen at 6 ms. The p -values indicated were obtained from a RM-ANOVA performed on the mean of the normalized MEP amplitudes. (B) Results of experiment 2 (right PMv conditioning prior to left M1 stimulation) are shown. (C) Results of the main experiment (sequential three single-pulse stimulation) are shown. MEP, motor-evoked potential; TMS, transcranial magnetic stimulation; PMv, ventral premotor cortex; M1, primary motor cortex; ISIs, interstimulus interval; RM-ANOVA, repeated-measures analysis of variance. *Statistically significant results were shown at ISIs of 4, 6, and 8 ms, indicating premotor-to-motor inhibition.

prior to conditioning of the ipsilateral PMv resulted in reversal of the resting premotor-to-motor inhibition (Fig. 3C).

DISCUSSION

The major conclusion of the current study is that the right PMv exerts an inhibitory influence on the left PMv, resulting in reversal of the resting premotor-to-motor inhibition seen in healthy human subjects at rest. We used a TMS paradigm that allowed us to assess the influence of the right PMv on the left PMv, using the premotor-to-motor inhibition as a conduit.

The inhibitory influence of the premotor cortex on the motor cortex has been demonstrated in several studies using paired-pulse paradigms. The anatomy of the connections between bilateral premotor cortices has been reported in studies on primates,^{13,19} but there are no reports of functional connectivity between these regions in human subjects. Such studies are possible with a triple-coil design.

It has previously been shown that in healthy human subjects, both PMv are involved in the movement preparation phase of the dominant (right) hand task, until the left hand is selected for movement.¹ Bilateral activation of the premotor cortices has also been shown in a fMRI study of human subjects performing unimanual object manipulation.²⁰ The callosal connections between bilateral PMv in human subjects have already been confirmed in diffusion tensor imaging.^{21,22} It is conceivable that the functional connectivity between bilateral premotor cortices that we observed reflects the cooperation of these two areas, which may be a component of bihemispheric control of manual tasks.

Although our findings clearly suggest transcallosal inhibition of bilateral premotor cortices, the physiology of this connectivity is not entirely clear, as previous reports to date are largely on ipsilateral connectivity. The transcallosal ventral premotor connection that we report is analogous to IHI of the motor cortex⁸ in healthy subjects. Studies have reported alterations in IHI in various patient populations, such as increased IHI in chronic stroke patients,^{23,24} prolonged IHI in patients with multiple sclerosis,²⁵ and reduced IHI in patients with writer's cramp²⁶ or Parkinson's disease.²⁷ In chronic stroke patients with good motor recovery, increased activation of the contralesional PMv was seen during skilled

manual task performance.²⁸ Therefore, the interhemispheric connectivity of bilateral PMv may be worth studying in these patient populations where various influences comprising the motor network may be altered. Such work will enable better understanding of the functional significance of the connectivity between the bilateral premotor cortices, known to be involved in motor control.

There are some limitations in our study. Due to the high number of pulses delivered, as a result of various stimulation intensities and ISIs used for each step of the experimental session, the experiments were not conducted in randomized blocks. This was necessary to establish appropriate stimulation parameters for the main experiment. The length of the experiment leads to two other concerns, possible decreased level of the subjects' alertness (i.e., sleepiness) throughout the session, and the potential residual effect of the high number of pulses. For concerns about coil movement, the experiments were conducted using a neuronavigation program real-time to ensure consistent coil placement on the bilateral PMv. Another limitation of our study is that as this was a novel paradigm, certain settings were determined experimentally, such as the current direction used to condition the contralateral PMv. This was determined as the anterior-to-posterior direction, in keeping with the current direction of the conditioning of ipsilateral PMv.

Further work can expand our understanding of the functional connectivity between these two homotopic regions. Investigation of the connectivity of the bilateral PMv in manual tasks will allow us to see if this connectivity is modulated during movement, suggesting that the cooperation of the two brain areas are involved in motor planning or execution. Investigation of this connectivity in the opposite direction (i.e., left PMv to right PMv) may also be valuable, as it is possible that the callosal connections may operate differently. It may be important to study this functional connectivity in patients with certain types of movement disorders (e.g., focal hand dystonia) whose problems appear to arise from deficient interactions involving the premotor cortex.^{29,30} Furthermore, past studies have found bilateral premotor activation in response to action observation of unilateral hand movement, as well as activation of both ipsi- and contralesional hemispheres in stroke patients following mirror therapy.^{31,32} The new knowledge that we present here adds to the current understanding of the role of premotor cortices

in motor control in healthy human subjects, and may have future therapeutic implications for neurological disorders involving difficulty with manual tasks, as well as motor rehabilitation.

Conflicts of Interest

The authors have nothing to declare.

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