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TMS activation of interhemispheric pathways between the posterior parietal cortex and the contralateral motor cortex

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Using a twin coil transcranial magnetic stimulation (tc-TMS) approach we have previously demonstrated that facilitation may be detected in the primary motor cortex (M1) following stimulation over the ipsilateral caudal intraparietal sulcus (cIPS). Here we tested the interhemispheric interactions between the IPS and the contralateral motor cortex (M1). We found that conditioning the right cIPS facilitated contralateral M1 when the conditioning stimulus had an intensity of 90% resting motor threshold (RMT) but not at 70% or 110% RMT. Facilitation was maximal when the interstimulus interval (ISI) between cIPS and M1 was 6 or 12 ms. These facilitatory effects were mediated by interactions with specific groups of interneurons in the contralateral M1. In fact, short intracortical inhibition (SICI) was reduced following cIPS stimulation. Moreover, additional comparison of facilitation of responses evoked by anterior–posterior *versus* posterior–anterior stimulation of M1 suggested that facilitation was more effective on early I1/I2 circuits than on I3 circuits. In contrast to these effects, stimulation of anterior IPS (aIPS) at 90% RMT induced inhibition, instead of facilitation, of contralateral M1 at ISIs of 10–12 ms. Finally, we found similar facilitation between left cIPS and right M1 although the conditioning stimuli had to have a higher intensity compared with stimulation of right cIPS (110% instead of 90% RMT). These findings demonstrate that different subregions of the posterior parietal cortex (PPC) in humans exert both facilitatory and inhibitory effects towards the contralateral primary motor cortex. These corticocortical projections could contribute to a variety of motor tasks such as bilateral manual coordination, movement planning in space and grasping.

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Abbreviations AMT, active motor threshold; CC, corpus callosum; EMG, electromyography; FCR, flexor carpi radialis; FDI, first dorsal interosseous; IPS, intraparietal sulcus; ISI, interstimulus interval; M1, primary motor cortex; MEP, motor evoked potential; PMd, dorsal premotor cortex; PPC, posterior parietal cortex; RMT, resting motor threshold; SICI, short intracortical inhibition; TMS, transcranial magnetic stimulation.

Although common everyday actions such as reaching and grasping an object appear as almost automatic processes, they require a complex interaction between different cortical areas. Non-primary motor regions such as the posterior parietal cortex (PPC) elaborate key information as to the optimal motor plan that has to be performed. In particular, the PPC is thought to code crucial information relevant for planning movements in space and to integrate visuo-motor transformations (Mountcastle *et al.* 1975; Kalaska *et al.* 1990; Kalaska &

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Crammond, 1995; Mountcastle, 1995; Johnson *et al.* 1996; Caminiti *et al.* 1996; Andersen & Buneo, 2002; Cohen & Andersen, 2002).

PPC is strongly interconnected with the premotor and motor cortices in the same hemisphere through distinct systems of fibres in the white matter that form part of the superior longitudinal fasciculus. We recently showed that it is possible to test these cortico-cortical connections in humans using a twin coil (or paired pulse) transcranial magnetic stimulation protocol (Koch *et al.* 2007*a*, 2008*a*,*b*). A conditioning TMS pulse is applied over PPC, shortly prior to a test pulse over the hand area of motor cortex (M1). The latter pulse evokes a small twitch in contralateral hand muscles that can be measured with surface EMG. When the interval between the PPC pulse and the M1 pulse is around 4–6 ms, the EMG response triggered by the M1 pulse is enhanced, indicating that the PPC pulse altered excitability of M1, and thus implying functional PPC–M1 connectivity. The site of the conditioning PPC pulse that led to the most pronounced impact on M1 lay over the caudal part of the intraparietal sulcus (cIPS), presumably activating a pathway that involves the superior longitudinal fasciculus (Koch *et al.* 2007*a*). Furthermore stimulation of another PPC region, situated over the anterior part of the intraparietal sulcus (aIPS), was found to activate an inhibitory projection toward ipsilateral M1 at the same intensity of stimulation (90% RMT) and ISI (4 ms) (Koch *et al.* 2007*a*).

The present study was designed to investigate whether it is possible to identify any interhemispheric connections between IPS and contralateral M1 using the same methodology. Indeed, previous studies have shown that interhemispheric connections can be activated between M1 and M1 and also between dorsal premotor cortex and M1 (Ferbert *et al.* 1992; Mochizuki *et al.* 2004; Bäumer *et al.* 2006; Koch *et al.* 2006, 2007*b*, 2008*c*). In the present series of experiments, a single magnetic pulse set at various intensities applied over the cIPS and the aIPS was followed at different interstimulus intervals (ISIs) by a TS delivered over the contralateral M1. Furthermore triple pulse experiments were carried out to determine the interactions of the interhemispheric projections with specific intracortical circuits of the contralateral M1 (see Fig. 1).

Methods

Subjects

Seventeen healthy volunteers (eleven men and nine women, 21–36 years old) participated in this study. All subjects were right handed based on the Edinburgh Handedness Inventory (Oldfield, 1971). Written informed

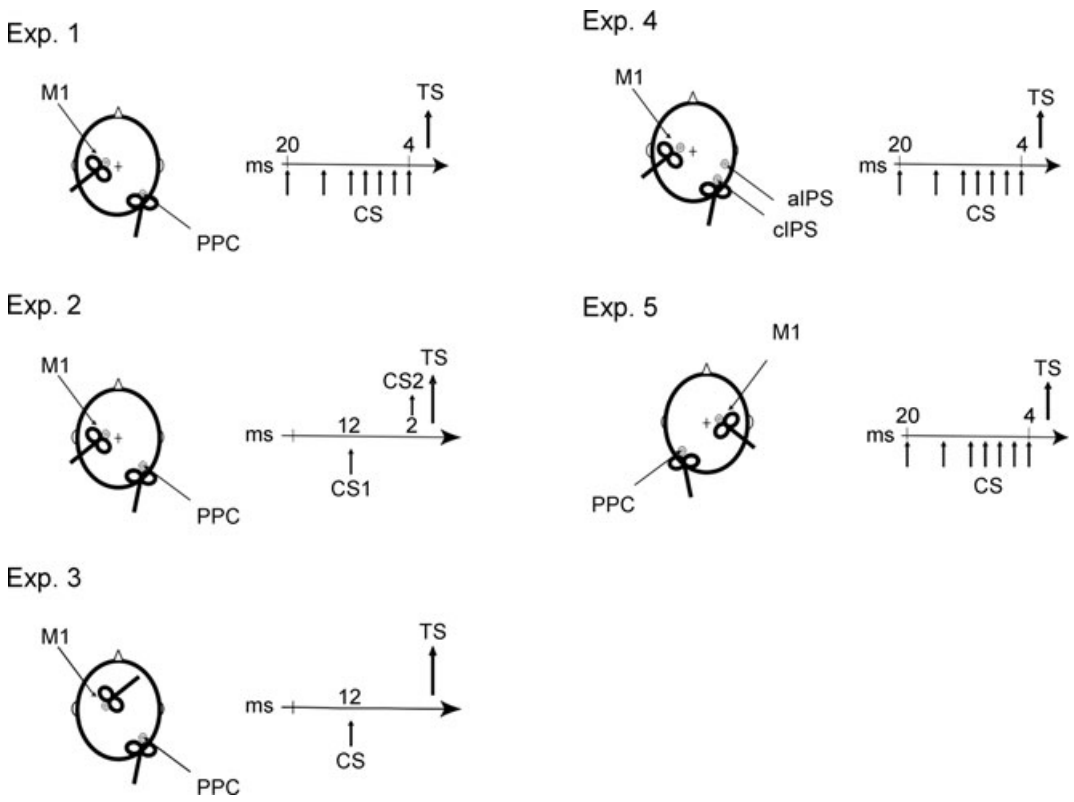

Figure 1. Schematic representation of the different experiments performed in the current study

consent was obtained from all subjects. The experimental procedures used here were approved by the local Ethics Committee at S. Lucia IRCCS and were carried out in accordance with the *Declaration of Helsinki*.

Experimental procedure

Electromyographic (EMG) traces were recorded bilaterally from the first dorsal interosseous (FDI) muscles using 9 mm diameter, Ag–AgCl surface cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified with a Digitimer D360 amplifier (Digitimer Ltd, Welwyn Garden City, UK) through filters set at 20 Hz and 2 kHz with a sampling rate of 5 kHz, then recorded by a computer using Signal software (Cambridge Electronic Design, Cambridge, UK). We analysed the onset latency of EMG in each trial.

Experiment 1. Interhemispheric interactions following right PPC stimulation at the cIPS

Eleven subjects participated in this experiment. We used a paired pulse stimulation technique with two high-power Magstim 200 machines (Magstim Co., Whitland, Dyfed, UK). First, the intensity of TS was adjusted to evoke a motor evoked potential (MEP) of approximately 1 mV peak to peak in the relaxed right FDI. The hand motor area of left M1 was defined as the point where stimulation evoked the largest MEP from the contralateral FDI muscle. The test stimulator was connected to a small custom-made figure-of-eight-shaped coil (external diameter 50 mm). The conditioning stimulator was connected to a normal figure-of-eight-shaped coil (external diameter 70 mm). The coil position for right cIPS was then defined relative to the P4 position of the 10–20 EEG system. According to previous investigations adopting 3D MRI reconstruction, this site is situated close over a part of the angular gyrus in the inferior parietal lobule and close to a posterior part of the adjoining intraparietal sulcus (cIPS) (Herwig *et al.* 2003; Rushworth & Taylor, 2006; Koch *et al.* 2007*a*). The centre of the coil was positioned over P4 tangential to the skull with the handle pointing downward and slightly posteriorly (10 deg) in order to induce a posterolateral–anteromedial current in the underlying cortical tissue. This orientation was chosen to be the same as that in our previous study of ipsilateral cIPS–M1 interactions; however we acknowledge that further experiments would be needed to test if this was optimal for revealing contralateral cIPS–M1 interactions (Koch *et al.* 2007*a*). The CS stimulus intensity was adjusted to be either suprathreshold (110% RMT) or subthreshold (90% and 70% RMT). We defined RMT as the lowest intensity that evoked five small responses (about 50 μV) in the left FDI muscle in a series of 10 stimuli when the subject kept the FDI muscles relaxed in both hands (Rossini *et al.* 1994). ISIs between CS and TS were 4, 6, 8, 10, 12, 15 and 20 ms. In each block we varied the intensity of the CS and the order of presentation of blocks varied pseudo randomly across subjects. Each block consisted of 90 trials. Eight conditions were randomly intermingled: TS alone (MEP) and CS1+TS (conditioned MEP for each seven different ISIs). Twenty responses were collected for test stimulus alone and 10 responses for conditioned MEP for each ISI. Measurements were made on each individual trial and the mean peak-to-peak amplitude of the conditioned MEP was also expressed as a percentage of the mean peak-to-peak amplitude size of the unconditioned test pulse.

Experiment 2. Effects of right cIPS conditioning on contralateral short-interval intracortical inhibition (SICI)

In six subjects (who also took part in experiment 1) we investigated the effects of a conditioning TMS pulse over right cIPS on short intracortical inhibition (SICI) circuits in the left M1, as evaluated using the paired pulse TMS protocol of Kujirai *et al.* (1993). For all the control experiments (exp. 2–4) we selected subjects that presented a strong cIPS–M1 facilitation in exp. 1. We used three high-power Magstim 200 machines: the first conditioning TMS pulse (CS1) was delivered at 90% RMT to the right PPC; the second conditioning TMS pulse (CS2) was applied over the left M1; and finally, the test TMS pulse (TS) was given over the left M1. The ISI between CS1 and TS was fixed at 12 ms, whilst the ISI between CS2 and TS was fixed at 2 ms. We set the intensity of CS2 to the relatively low value of 80% active motor threshold (AMT). Although performing a SICI curve would be the optimal procedure to avoid ceiling/floor effects, the adopted intensity (80% AMT) usually produces a stable SICI of about 50–60%, a value that reduces the possibility of ceiling/floor effects (Mochizuki *et al.* 2004). We defined the AMT as the lowest intensity that evoked five small responses (about 100 μV) in a series of 10 stimuli when the subject made a 5% MVC (about 50 μV) of the right FDI (Rothwell, 1997).

The effects of PPC conditioning on motor cortex SICI were tested in three different experimental sessions.

In the first session, the intensity of TS was adjusted to evoke a MEP of approximately 1 mV peak to peak in the relaxed right FDI, as in experiment 1. We then tested the effects on the amplitude of the test MEP of giving CS1 alone (PPC facilitation), CS2 alone (SICI) and the combined effect of CS1+CS2.

The aim of the first set of experiments was to test how CS1 affected the amount of SICI produced by CS2. However, since CS1 also facilitated the test MEP when

applied alone, it is difficult to interpret its effects on SICI (i.e. when CS1+CS2 were applied together). In a second session we tried to control for this effect on the test MEP by reducing the intensity of the TS in order to induce a MEP decrease of ∼30% (0.7 mV), so that when CS1 was applied, the combined effect would elicit a MEP of ∼1 mV. CS2 effects (SICI) and CS1+CS2 interactions were then tested, to verify how much CS1 would change MEP amplitude when SICI circuits were activated (CS1+CS2).

Finally in a third session, in order to control for inhibitory effects of CS2, the intensity of TS was increased in order to induce a larger baseline MEP (approx 2 mV), so that CS2+TS would induce a MEP of ∼1 mV. We could then confirm that CS1 still facilitated a MEP of this size when applying CS1+CS2 prior to TS.

Three conditions were intermixed randomly in each block (TS alone, control; CS2 and TS; CS1 and TS; CS1, CS2 and TS). Ten responses were collected in each condition. Measurements were made on each individual trial and the mean peak-to-peak amplitude of the conditioned MEP was also expressed as a percentage of the mean peak-to-peak amplitude of the unconditioned test pulse.

Experiment 3. Effects of right cIPS conditioning on responses evoked by different current directions over M1

To gain additional evidence about the I wave projections in M1 targeted from cIPS, we tested, in six subjects (who also participated in experiment 1), the effect of CS given over the right cIPS on TS produced by an anterior–posterior (AP) current flow in the left M1 by rotating the TS coil by 180 deg such that it was positioned 45 deg rotated towards the midline (Bäumer *et al.* 2006). In fact it has been previously shown that AP-directed TMS pulses lead to activation of the corticospinal tract preferentially by inducing I3 waves whereas PA-directed currents preferentially activate early waves (Sakai *et al.* 1997; Hanajima *et al.* 2001).

In this experiment MEPs obtained with PA orientation were preceded half the time by a CS applied over the right cIPS at 90% RMT with an ISI = 12 ms. cIPS conditioning in the AP orientation was delayed by 1.5 ms (13.5 ms) to give coincidence of the CS arrival effects at the M1 during generation of later I waves (onset approximately 1.5 ms later than I1/I2.) The intensity of TS was adjusted to evoke a MEP of approximately 1 mV peak to peak in the relaxed right FDI. Ten responses were collected in each condition.

Experiment 4. Interhemispheric interactions following right PPC stimulation at the cIPS *vs.* aIPS

In this experiment ($n = 6$, all participated in experiment 1) we compared the effect of stimulation of cIPS with another subregion of the PPC, the aIPS. We choose to stimulate this specific area to confirm that the effects observed with cIPS stimulation were site specific and because we had already shown that aIPS stimulation was able to activate inhibitory projections over the ipsilateral M1 and was therefore selected as a putative area interconnected with M1 (Koch *et al.* 2007*a*). In this experiment we used neuronavigation system (Softaxic, E.M.S., Bologna, Italy) to position the coil precisely over the stimulation sites, using individual anatomical magnetic resonance images; this technique has been described in detail previously (Noirhomme *et al.* 2004; Davare *et al.* 2007). The individual coordinates of each stimulation site were normalized *a posteriori* into the Montreal Neurological Institute (MNI) coordinate system and averaged. To target aIPS, the coil was positioned close to the intersection between the intraparietal sulcus and postcentral sulcus. The centre of the coil was positioned tangentially to the skull with the handle pointing downward and slightly medial (10 deg) in order to induce a posterior–anterior directed current in the underlying cortical tissue. To target cIPS, the coil was positioned over a part of the angular gyrus in the inferior parietal lobule and close to a posterior part of the adjoining intraparietal sulcus (cIPS) (Herwig *et al.* 2003; Rushworth & Taylor, 2006; Koch *et al.* 2007*a*). The centre of the coil was positioned tangentially to the skull with the handle pointing downward and slightly medial (10 deg) in order to induce a posterior–anterior directed current in the underlying cortical tissue.

In two separate blocks CS was applied over the right cIPS or the right aIPS. The CS stimulus intensity was adjusted to be 90% RMT. ISIs between CS and TS were 4, 6, 8, 10, 12, 15 and 20 ms. TS was applied over the left M1. The intensity of TS was adjusted to evoke a MEP of approximately 1 mV peak to peak in the relaxed right FDI. Each block consisted of 90 trials. Eight conditions were randomly intermingled: TS alone (MEP) and CS1+TS (conditioned MEP for each 7 different ISIs). Twenty responses were collected for test stimulus alone and 10 responses for conditioned MEP for each ISI.

Measurements were made on each individual trial and the mean peak-to-peak amplitude of the conditioned MEP was also expressed as a percentage of the mean peak-to-peak amplitude size of the unconditioned test pulse.

Experiment 5. Interhemispheric interactions following left PPC stimulation

Eleven subjects (5 of whom took also part in exp. 1) participated in this experiment. To stimulate right M1 the intensity of TS was adjusted to evoke a MEP of approximately 1 mV peak to peak in the relaxed left FDI. The CS coil was positioned similarly as in exp. 1 over

left cIPS. The CS stimulus intensity was adjusted to be either suprathreshold (110% RMT) or subthreshold (90% RMT). For this experiment RMT was assessed in the left hemisphere. ISIs between CS and TS were 4, 6, 8,10, 12, 15 and 20 ms. In each block we varied the intensity of the CS and the order of presentation of blocks varied pseudo randomly across subjects. Each block consisted of 80 trials. Seven conditions were randomly intermingled: TS alone (MEP) and CS1+TS (conditioned MEP for each seven different ISIs). Twenty responses were collected for test stimulus alone and 10 responses for conditioned MEP for each ISI. Measurements were made on each individual trial and the mean peak-to-peak amplitude of the conditioned MEP was also expressed as a percentage of the mean peak-to-peak amplitude size of the unconditioned test pulse.

Experiment 6. Effects of stimulating right PPC on the H reflex evoked by median nerve stimulation

Six subjects participated in this control experiment. We tested in this experiment whether right PPC conditioning could modulate spinal circuits measured through the H reflex from the right flexor carpi radialis (FCR). The excitability of the monosynaptic H-reflex in the left FCR motoneurons was tested with a standard technique (Hortobágyi *et al.* 2003). Single electrical stimuli were delivered with saline-soaked gauze-covered button electrodes, the cathode 5 cm proximal to the anode, in the cubital space (duration 1 ms, Digitimer DS7) with the subject at rest. First, we determined the appropriate stimulating electrode location and identified the H-reflex in the FCR based on its latency and recruitment curve. Next, we increased stimulation intensity to produce a maximal compound action potential. The median nerve stimulation intensity was set to produce an H-reflex that corresponded to an amplitude of 1 mV. The intensity of the left PPC CS was adjusted to be 90% RMT. The intensity of motor cortex stimulation was set to produce a MEP recorded from the right FCR that corresponded to an amplitude of 1 mV. There were four conditions: (1) MEPs recorded after stimulation of the hot spot of the FCR; (2) MEP conditioned by right PPC CS using an ISI between CS and TS of 12 ms; (3) FCR H-reflex with the time of the median nerve stimulus arranged to produce an H-reflex with the same latency as the MEP; (4) FCR H-reflex conditioned by right PPC CS using an ISI of 16 ms, in order to precede by 12 ms the FCR H-reflex with the time of the median nerve stimulus arranged for the same latency as the MEP (Koch *et al.* 2007*a*). Twenty responses were collected in each condition. Measurements were made on each individual trial on the peak-to-peak amplitude of the H reflex recorded from FCR.

Data analysis

In experiments 1 and 5, the effects of PPC CS on the size of MEP recorded from stimulation of contralateral M1 were analysed with repeated measures ANOVAs with INTENSITY (70% *vs.* 90% *vs.* 110% RMT) and ISI (4 *vs.* 6 *vs.* 8. *vs.* 10 *vs.* 15 *vs.* 20 ms) as main factors using normalized values calculated as the percentage of the mean peak-to-peak amplitude size of the unconditioned test pulse. In experiment 2 we performed repeated measure ANOVA with block (TS at 1 mV, CS1-TS adjusted; CS2-TS adjusted) and CONDITION (TS alone *vs.* CS2 and TS *vs.* CS1, CS2 and TS) as main factors. In experiment 4 we performed repeated measures ANOVAs with SITE (cIPS *vs.* aIPS) and ISI as (4 *vs.* 6 *vs.* 8. *vs.* 10 *vs.* 15 *vs.* 20 ms) as main factors. A significant main effect by ANOVA was followed by *post hoc* analysis by Student's *t*-test for paired data with Bonferroni's correction of *P* according to the number of comparisons made. The Greenhouse–Geisser correction was used for non-spherical data.

Results

Experiment 1

Our major finding in experiment 1 was that conditioning stimuli over the right cIPS facilitated contralateral motor cortex at specific intervals and intensities.

This was confirmed by a two-way ANOVA performed on normalized values that showed significant main effects of ISI ($F = 7.13$; $P < 0.05$) as well a significant INTENSITY × ISI interaction ($F = 3.82$; $P < 0.05$). *Post hoc* analyses showed that CS = 90% RMT intensity resulted in significant facilitation at ISI = 6 ms in comparison with both 70% RMT (paired *t*-test; $t = 3.14$, $P = 0.008$; accepted Bonferroni corrected P value = 0.016) and 110% RMT (paired *t*-test; $t = 3.03$, $P = 0.009$; accepted Bonferroni corrected P value = 0.016). At ISI = 8 ms facilitation at 90% RMT was greater than at 110% RMT (paired *t*-test; $t = 3.05$, $P = 0.009$; accepted Bonferroni corrected P value = 0.016) whilst at ISI = 12 ms it was greater in comparison with both 70% RMT (paired *t*-test; $t = 2.84$, $P = 0.012$; accepted Bonferroni corrected P value = 0.016) and 110% RMT (paired *t*-test; $t = 3.51$, $P = 0.004$; accepted Bonferroni corrected P value = 0.016) (Fig. 2). This result was confirmed with subsequent paired *t*-test analysis performed on mean MEP amplitude values: thus for CS = 90% RMT, MEPs were increased in comparison with the TS at ISIs of 6 ms (mean ± standard deviation of the mean = 1.64 ± 0.58 *vs.* 1.31 ± 0.35 mV; $P < 0.05$), 8 ms (1.61 ± 0.56 *vs.* 1.31 ± 0.35 mV; $P < 0.05$) and 12 ms (1.62 ± 0.58 vs.1.31 ± 0.35 mV; $P < 0.05$). No significant effect was obtained when the intensity was set either at 70% or 110% RMT.

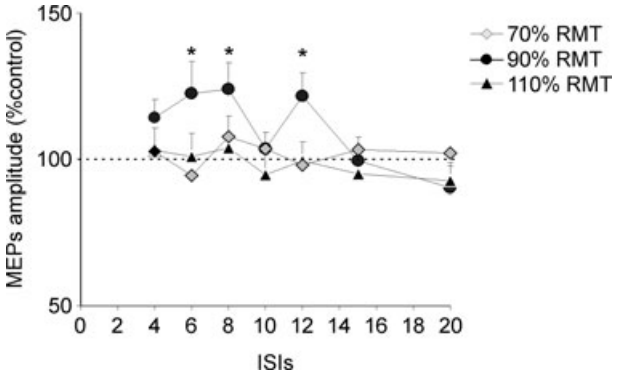

Figure 2. Effects of CS applied over right cIPS at different intensities on MEPs obtained by left M1 stimulation with subjects at rest
CS preceded TS applied over M1 by different ISIs ranging from 20 to 4 ms. Data are normalized and expressed as percentage of control test condition. Errors bars indicate 1 S.E.M. Asterisks indicate a P value < 0.05 at *post hoc* analysis.

Experiment 2

In this experiment we investigated possible effects of conditioning stimulation over right cIPS (90% RMT) on SICI circuits in the left M1. A repeated measures ANOVA revealed a significant main effect of CONDITION ($F = 8{,}39$; $P < 0.01$), but no CONDITION × BLOCK interaction. Thus, SICI was significantly reduced after PPC stimulation for all the different TS intensities that we had used (all $P < 0.05$ at t-test analysis). In fact, stimulation of cIPS increased the amplitude of the response to the M1 test pulse by some 40%, while baseline SICI, which in the absence of cIPS conditioning was 60% of the control MEP amplitude, was almost abolished after PPC stimulation (Fig. 3).

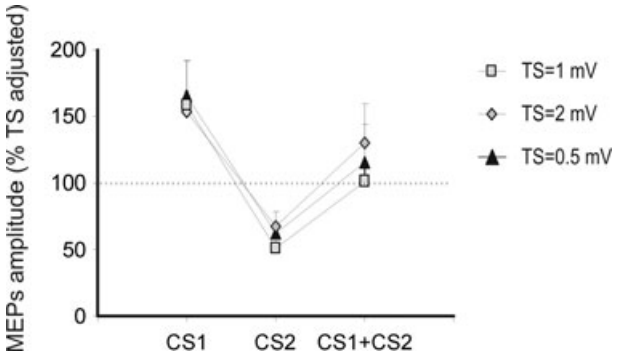

Figure 3. Effects of right cIPS conditioning on the strength of SICI circuits (ISI = 2 ms) in contralateral M1
TS was set at different intensities. In the first block the intensity of TS was adjusted to evoke a MEP of approximately 1 mV peak to peak in the relaxed right FDI, as in experiment 1. In a second block TS intensity was reduced to elicit a facilitated CS1-TS of ∼1 mV MEP, in order to control for CS1-TS facilitatory effects. In a final block we increased the intensity of TS to obtain a CS2-TS of ∼1 mV MEP, in order to control for CS2-TS inhibitory effects. Errors bars indicate 1 S.E.M.

Experiment 3

To provide some information as to what I-wave inputs might be preferentially targeted by the actions of cIPS on M1, we tested the effect of CS given over the right cIPS on TS produced by an anterior–posterior (AP) current flow in the left M1 by rotating the TS coil by 180 deg. As expected, latencies of MEPs evoked with AP were longer than those induced by posterior–anterior (PA) TS orientation (25.6 ± 1.4 *vs.* 23.9 ± 1.2; $t = -3.18$; $P = 0.03$). We observed that facilitation of MEPs following cIPS stimulation (90% RMT; ISI = 12 ms) was evident only when the coil for M1 stimulation was applied with PA (1.31 ± 0.19 *vs.* 1.70 ± 0.20 mV; $t = -3.36$; $P = 0.03$) but not when it was applied with AP orientation (1.22 ± 0.18 *vs.* 1.21 ± 0.16 mV; n.s.). To directly compare the effects of TS with different orientations we also performed a paired t-test on the percentage of increase in the MEP amplitude in trials with the PPC stimulation, which showed a significant difference (130.8 ± 7.52 *vs.* $99.9 \pm 4.27\%$; $t = 3{,}45$; $P = 0.02$) (Fig. 4).

Experiment 4

In the present study, the mean normalized MNI coordinates of aIPS stimulation sites were, respectively, 43.4 ± 8.4, -38.2 ± 6.6 and 47.0 ± 5.2 mm (x, y, z, mean ± S.D.). These coordinates overlapped the location of aIPS reported by TMS and fMRI studies in humans (Binkofski *et al.* 1999; Ehrsson *et al.* 2001; Davare *et al.* 2007). The mean normalized MNI coordinates of cIPS stimulation sites were, respectively, 22.7 ± 6.7, -67.8 ± 5.3 and 54 ± 3.2 mm (x, y, z, mean ± S.D.) overlapping the location of cIPS reported by previous studies in humans (Shikata *et al.* 2001). The aIPS site was found to be approximately 4.5 cm anterior and 1 cm lateral to the cIPS site.

We observed that stimulation of cIPS and aIPS (Fig. 5*A* and *B*) had different effects on the excitability of

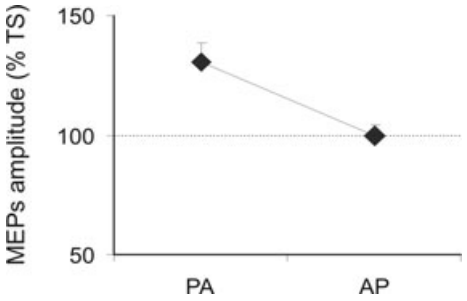

Figure 4. MEP amplitudes (mean values ± S.E.M.) for M1 stimulation with AP or PA orientation alone and when preceded by a CS applied over the right cIPS (90% RMT at ISIs of 12 ms)
*$P < 0.05$. AP, anterior–posterior current flow of the TMS test pulse; PA, posterior–anterior current flow of the TMS test pulse.

contralateral M1. While cIPS induced facilitation, aIPS induced inhibition, peaking at ISI = 10 ms (Fig. 5*C*). This was borne out in the ANOVA, which showed a significant main factor of SITE ($F = 26{,}8$; $P < 0.01$) and ISI ($F = 3{,}12$; $P < 0.05$) as well a significant SITE × ISI interaction ($F = 2{,}98$; $P < 0.05$). This result was confirmed with subsequent paired *t*-test analysis performed on mean MEP amplitude values. cIPS stimulation increased MEPs in comparison with responses to the test stimulus alone at ISIs of 6 ms (1.20 ± 0.36 mV *vs.* 0.95 ± 0.25 mV; $P < 0.05$) and 12 ms (1.22 ± 0.39 mV *vs.* 0.95 ± 0.25 mV; $P < 0.05$). For aIPS in comparison with TS there was a significant reduction of MEP amplitude at ISI = 10 ms (0.78 ± 0.32 *vs.* 1.01 ± 0.39) and 12 ms (0.83 ± 0.29 *vs.* 1.01 ± 0.39).

Experiment 5

Possible effects induced by *left* cIPS stimulation on contralateral M1 were investigated in this experiment. Again we found that left cIPS conditioning facilitated contralateral M1, although this required a higher intensity of stimulation than after stimulation of right cIPS.

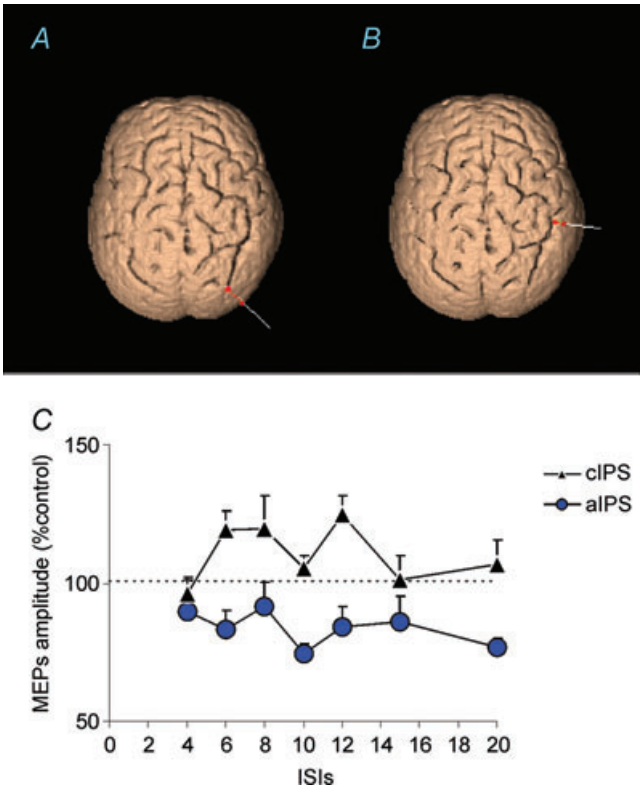

Figure 5. Different effects of right aIPS and cIPS conditioning (intensity = 90% RMT) on contralateral M1 excitability
Coil position for stimulation of aIPS (*A*) and cIPS (*B*) were determined using neuronavigation system in a representative subject. Errors bars indicate 1 S.E.M. **P* value < 0.05 at *post hoc* analysis.

This was confirmed in the two-way ANOVA performed on normalized values, showing a significant INTENSITY × ISI interaction ($F = 2{,}42$; $P < 0.05$). *Post hoc* analysis showed that CS = 110% RMT intensity induced significant facilitation at ISI = 6 ms in comparison with CS = 90% RMT intensity (paired *t*-test; $t = 2.65$, $P = 0.012$; accepted Bonferroni corrected *P* value = 0.025). A significant facilitation was also observed at an intensity = 110% RMT and ISI = 12 ms in comparison with CS = 90% RMT intensity (paired *t*-test; $t = 3.05$, $P = 0.012$; accepted Bonferroni corrected *P* value = 0.025) (Fig. 6). Subsequent paired *t*-test analysis showed that mean MEP amplitudes following a CS = 110% RMT were increased in comparison with the TS at ISIs of 6 ms (1.14 ± 0.48 *vs.* 0.97 ± 0.45 mV; $P < 0.05$) and 12 ms (1.18 ± 0.56 *vs.* 0.97 ± 0.45; $P < 0.05$).

Experiment 6

In this control experiment we observed that a right PPC CS did not change the amplitude of the H reflex recorded from right FCR (1.12 ± 0.21 *vs.* 1.09 ± 0.18 mV; $t = 0.65$) while it significantly increased the amplitude of the FCR MEP (0.98 ± 0.32 *vs.* 1.22 ± 0.36 mV; $t = 0.03$). To directly compare the effects of PPC CS on the H reflex and MEP FCR, we also performed a paired *t*-test on the percentage of increase in the H reflex *versus* the FCR MEP amplitude in trials with the PPC stimulation, revealing a significant difference (101.3 ± 0.08 *vs.* 118 ± 0.13%; $t = 2.98$; $P = 0.04$).

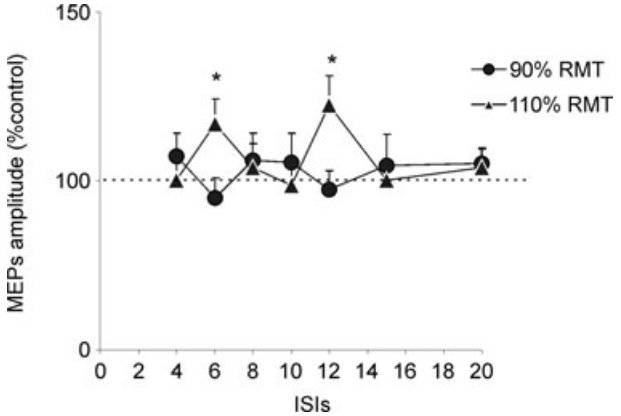

Figure 6. Effects of CS applied over left cIPS at different intensities on MEPs obtained by right M1 stimulation
CS preceded TS applied over M1 by different ISIs ranging from 20 to 4 ms. Data are normalized and expressed as percentage of control test condition. Errors bars indicate 1 S.E.M. Asterisks indicate a *P* value < 0.05 at *post hoc* analysis.

Discussion

We found that magnetic stimulation of PPC activates different facilitatory or inhibitory interhemispheric pathways depending on the site and on the intensity of stimulation. Thus, conditioning stimuli over right cIPS facilitated contralateral motor cortex whereas stimuli over right aIPS suppressed it. Both effects were best observed at intensities of 90% RMT and had a biphasic time course that peaked at ISIs of 6 and 12 ms. cIPS stimulation was also able to decrease SICI in contralateral M1. Indeed, experiments with different orientations of the test coil over motor cortex suggest that the facilitatory effect was mainly onto early I wave inputs activated preferentially by PA induced current in the brain. Finally, although we observed a symmetrical facilitation between left cIPS and right motor cortex, it required a slightly higher intensity of conditioning stimulus (110% RMT). We argue that these interactions are likely to be due to activation of transcallosal connections between the hemispheres, and that they may be involved in bilateral visuomotor hand coordination. They may represent an interhemispheric homologue of the within hemisphere projections from PPC to M1 that we have described in a previous paired pulse TMS study (Koch *et al.* 2007*a*).

Interhemispheric pathways between PPC and M1

MEPs evoked by TMS over M1 are thought to be primarily mediated via direct corticomotoneuronal projections to spinal cord motoneurones so that any changes in amplitude of the response following conditioning stimulation of PPC must be due to changes in synaptic transmission at the spinal cord or at the motor cortex. There are no direct ipsilateral projections from PPC that might mediate an effect at spinal level although we cannot exclude an indirect projection via PPC projections to pons and thereby to spinal cord via bilateral reticulospinal connections. Nevertheless it seems more likely that the interaction we describe involves cortico-cortical effects transmitted via the corpus callosum.

Anatomical studies show that different subregions of the PPC are strongly interconnected with the contralateral hemisphere via transcallosal projections. For instance, a recent diffusion tensor imaging (DTI) study showed that the location of fibres in the corpus callosum (CC) followed the antero-posterior location of their cortical connections (Zarei *et al.* 2006). Connections of the prefrontal cortex were located within the genu and anterior part of the body. Premotor cortical connections were located in the mid body region. Immediately posterior to the premotor region were M1 tracts, followed by somatosensory (S1) tracts. Posterior parietal cortical connections were predominantly observed posterior to S1. Finally tracts connecting to temporal cortices occupied a considerable proportion of the splenium and the occipital tracts form the most posterior part of the splenium (Zarei *et al.* 2006). This DTI map is consistent with callosal fibre distributions defined in post-mortem studies (Pandya *et al.* 1971; Witelson, 1989). According to Witelson's classification, bundles originating from the PPC form part of the isthmus of the CC (region IV). However a new DTI-based fibre tractography classification of healthy human subjects suggests a modification of the widely accepted Witelson scheme and a new classification of vertical CC partitions (Hofer & Frahm, 2006). In this context, callosal parietal, temporal, and occipital fibres cross the CC through region V, which is defined as the posterior one-fourth.

While dense connections are regularly observed between homologous regions of the two hemispheres, studies in monkeys of callosal connectivity of posterior parietal cortex have revealed that there are a smaller number of transcallosal connections not only with homologous parietal areas but also with motor areas of the neocortex as well as with body part representations in somatosensory areas (Pandya & Vignolo, 1969; Pandya *et al.* 1971; Jones *et al.* 1979; Killackey *et al.* 1983; Shanks *et al.* 1985; Neal, 1990). Such connections could form the substrate for interhemispheric transfer of information necessary for bilateral limb and hand coordination (Padberg *et al.* 2005).

On the basis of this theoretical background, we hypothesize that, in our study, the effects observed within the motor cortex following contralateral cIPS or aIPS stimulation may reflect activation of either direct transcallosal fibres connecting PPC–M1 or activation of indirect pathways involving the homologous parietal regions and thence to motor cortex or conversely the ipsilateral and then the contralateral motor cortex. Indeed it could even be that the direct projection is responsible for the early (6 ms) peak of interaction whereas the indirect projection is responsible for the later (12 ms) peak.

Other interhemispheric inputs to M1 have been described in previous studies, from the homologous M1 (Ferbert *et al.* 1992), from the dorsal premotor cortex (Mochizuki *et al.* 2004), and from the somatosensory and the dorsolateral prefrontal cortex (Ni *et al.* 2008). The most robust effect in both instances was inhibitory with an early phase at latency of 8–10 ms, and with a later peak at approximately 50 ms (Ni *et al.* 2008). These two related phases are thought to depend on the activity of different neuronal populations (Ni *et al.* 2008). Although we did not verify this hypothesis, it is possible that similar interactions could also be observed between the PPC and contralateral M1 at longer latencies.

Other studies showed that it was also possible to identify an earlier (around 4–6 ms) facilitatory interaction (M1: Hanajima *et al.* 2001; PMd: Bäumer *et al.* 2006) that was only seen with lower intensities of conditioning stimuli. It is unclear why inhibition predominates in

interhemispheric connections from M1 and PMd (as well as aIPS) whereas that from cIPS is predominantly facilitatory. It may relate simply to the relative electrical thresholds of the systems in each cortical area, or it may be a function of the excitability of any interneurones in the connection pathway.

Interactions with M1 intracortical circuits

While the exact pathways transferring the information from the cIPS to the contralateral M1 cannot be established, the study with different orientations of test coil over M1 suggests that the input from contralateral cIPS targets particular subsets of inhibitory and excitatory inputs to the corticospinal neurons.

First, we observed that PPC stimulation at 90% RMT was able to decrease SICI in contralateral M1. Interestingly, analogous effects have been reported for PMd stimulation at similar intensities (Mochizuki *et al.* 2004) and for M1 stimulation, although at much higher intensities (Daskalakis *et al.* 2002).

It should be noted that there are no known long-range inhibitory neurones that cross the corpus callosum (Kukaswadia *et al.* 2005), so that we speculate that the effect involves activation of an inhibitory interneurone in the receiving M1. It is known that facilitatory trans-callosal cortico-cortical fibres reach a population of different classes of GABAergic inhibitory neurones in the cortex with distinct pharmacological properties that have different connectivity and interact differentially with pyramidal neurones (Xiang *et al.* 1998, 2002; Reis *et al.* 2008). Therefore it is likely that the observed effects of PPC stimulation on contralateral SICI are mediated by similar interactions, reducing the activity of GABAergic interneurons involved in SICI circuits (see Fig. 7).

Secondly, we observed that PPC stimulation differently modulated the groups of interneurons involved in the generation of descending I-waves (Amassian & Stewart 2003). These findings are in line with previous investigations in monkeys, showing that cortico-cortical facilitatory inputs to M1 impinge on interneurons generating corticospinal I waves (Shimazu *et al.* 2004). The present data, in conjunction with previous work, indicate that these interactions can be specific to particular I wave inputs. Thus, there was significant facilitation if the coil over M1 was applied with a PA, but not an AP orientation. Since the former tends to activate early and late I waves, and the latter targets late inputs (Hanajima *et al.* 2002), the implication is that the facilitation occurs mainly through excitation of I1/I2 pathways. However it is important to note that we do not claim that this is a completely rigid distinction. The preferential sensitivity of different I waves to coil orientation is best observed in studies that use active muscles and small MEPs in order to employ just-suprathreshold stimulus intensities. At the higher test intensities that we used in the present study on resting muscles, there is likely to be a far less pure distinction between recruitment of I1 and I3 (e.g. Hanajima *et al.* 2002). Moreover we did not systematically test the effects induced by PA and AP at different ISIs.

However, it is interesting to note that facilitatory input from contralateral dorsal premotor areas also appears to target the same early I waves, since it too is most powerful when using a PA orientation (Bäumer *et al.* 2006). In contrast, we previously found that the ipsilateral inputs from PPC targeted late I waves rather than early I waves (Koch *et al.* 2007*a*). The difference may relate to the fact that the main site of termination of ipsilateral cortico-cortical fibres is in layer IV of the cortex whereas trans-callosal inputs target layer III. Even so it is possible that facilitatory input originating from contralateral PPC may directly activate interneurons involved in the generation of early I-waves (see Fig. 7).

Left–right asymmetry of cIPS–M1 interhemispheric pathways

Another interesting finding of the current study is that different intensities of stimulation were needed to activate

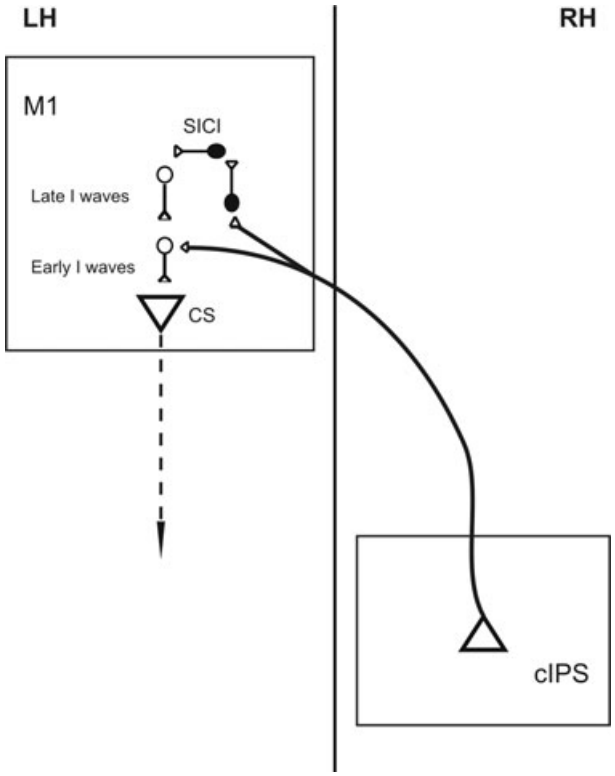

Figure 7. Hypothetical pathways mediating interhemisperic facilitation between PPC and contralateral M1
Facilitatory interhemispheric output from cIPS could synapse onto contralateral inhibitory (filled circles) and excitatory (open circles) M1 interneurons, modulating both SICI and early I waves circuits.

the cIPS–contralateral M1 pathway in the two hemispheres. While stimulation of right cIPS at 90% RMT was sufficient to increase contralateral M1 excitability, higher intensities (110% RMT) were necessary to have the same effect from left cIPS. This is unlikely to be due to anatomical differences between the hemispheres that alter the relative stimulation thresholds relative to motor threshold since the threshold for within hemisphere PPC–M1 interactions is the same on the right and left sides (Koch *et al.* 2007*a*). It is possible that it relates in some way to the asymmetry of the human spatial attention system that is well documented in both disease and healthy states: right hemisphere (RH) lesions are more frequently associated with hemispatial neglect compared with left-hemisphere (LH) lesions and usually cause more severe and persistent deficits (Mesulam, 1999); moreover, a leftward bias in the perception of contralateral targets, termed right 'pseudoneglect', is frequently reported in healthy subjects (Orr & Nicholls, 2005). Thus a lower threshold for right cIPS–left M1 might be associated with this right hemisphere dominance. Further investigations, for example in patients with neglect symptoms, are needed to clarify this issue (Koch *et al.* 2008*d*). In this regard, it is important to note that other systems with a clear behavioural lateralization, such as the motor system, do not necessarily show electrophysiological laterality.

There are a number of limitations to our study. The first involves the effects that we saw from the aIPS conditioning stimulus. Even though we used a subthreshold CS, we cannot exclude the possibility that some of the effects were due to spread of the magnetic stimulus to the adjacent somatosensory cortex, especially since neuronavigation systems were not employed. The second limitation is that relatively small numbers of subjects were used, so that conclusions based on lack of an effect are weak given the possibility of a type II error.

Physiological role of interhemispheric connectivity

It has been proposed that in monkeys interhemispheric connections between the posterior parietal cortex and the contralateral motor system could form the substrate for interhemispheric transfer of information necessary for bilateral limb and hand coordination (Padberg *et al.* 2005; Grefkes & Fink 2005). Furthermore in a recent work in humans we showed that cIPS–ispilateral M1 functional connectivity is specifically activated during reaching movements towards contralateral but not ipsilateral targets (Koch *et al.* 2008*a*), suggesting that these facilitatory interactions are crucial during movement planning in space. Although this hypothesis remains speculative, cIPS–contralateral M1 connectivity could play a similar role in orchestrating bilateral reaching movements in space. The role of aIPS may be subtly different: aIPS is thought to be part of a 'grasping circuit' together with the ventral premotor cortex (PMv) (see Olivier *et al.* 2007 for a review). Electrophysiological studies in monkeys (Murata *et al.* 2000; Umiltà *et al.* 2007) together with functional neuroimaging and TMS studies in humans (Davare *et al.* 2007; Tunik *et al.* 2005; Glover *et al.* 2005) have shown that this area is responsible for processing visuospatial information about the object that has to be grasped. Consequently we may hypothesize that aIPS–contralateral M1 connectivity could be involved in similar tasks, although this has to be confirmed in dedicated studies.

In conclusion we have demonstrated that different subregions of the PPC influence the excitability of contralateral M1 through probable transcallosal pathways. These corticocortical projections could contribute to a variety of motor tasks such as bilateral manual coordination, movement planning in space and grasping. Future behavioural studies could be used in conjunction with the present technique to reveal the time course of causal interactions in the interhemispheric PPC–M1 connections, while information on their anatomical basis could be obtained by combining twin coil TMS with structural neuroimaging techniques, such as diffusion tensor imaging (DTI), an MRI technique that permits the tracing of white matter pathways as well as by studies in patients with lesions of the CC.

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Author contributions

G.K., D.R., B.C., M.F.O. and J.C. conceived and designed the experiment; G.K., E.L.G., S.T., V.V., C.P. and B.M. carried out the experiments; G.K. and M.O. performed data analysis; G.K. and J.C. wrote the paper; M.O. and C.C. revised the paper. Experiments were carried out in the TMS laboratory at S. Lucia IRCCS, Rome.

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