

The effects of inhibitory and facilitatory intracortical circuits on interhemispheric inhibition in the human motor cortex

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Inhibitory and facilitatory intracortical pathways regulating motor cortical output can be studied non-invasively in humans with transcranial magnetic stimulation. These circuits include short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI) and intracortical facilitation (ICF). Stimulation of the motor cortex also inhibits the contralateral motor cortex (interhemispheric inhibition, IHI) at short (~ 10 ms, IHI10) or long intervals (~ 40 ms, IHI40). We investigated how SICI, ICF, and LICI influence IHI10 and IHI40. We hypothesize that intracortical circuits will have similar effects on IHI and cortical output neurons: SICI and LICI will decrease IHI, and ICF will increase it. Motor evoked potentials were recorded from the first dorsal interosseous muscles bilaterally in 10 healthy subjects. We compared IHI10 and IHI40 alone to IHI10 and IHI40 elicited in the presence of SICI, ICF, or LICI. Our results showed that SICI and LICI reduced IHI10, IHI40 and corticospinal output to a similar degree. ICF increased corticospinal output but had no effect on either IHI10 or IHI40. The different effects of ICF on corticospinal excitability and IHI suggest the transcallosal fibres mediating IHI and the corticospinal output system arise from different neuronal populations. SICI and LICI produce more global inhibition with similar effects on the transcallosal and descending corticospinal circuits.

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Transcranial magnetic stimulation (TMS) can be used to study different inhibitory and excitatory circuits in the human motor cortex (Rothwell, 1997; Hallett, 2000; Chen, 2004). Two types of cortico-cortical inhibition are short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI). SICI is elicited by a subthreshold conditioning stimulus (CS) followed by a test stimulus (TS) at interstimulus intervals (ISI) of 1–6 ms (Kujirai *et al.* 1993; Chen *et al.* 1998). LICI differs with respect to stimulus strength and ISI requiring a suprathreshold CS at an ISI of 50–200 ms (Valls-Sole *et al.* 1992; Wassermann *et al.* 1996). It is thought that SICI is mediated by GABA_A receptors (Ziemann *et al.* 1996a; Hanajima *et al.* 1998) while LICI is mediated by GABA_B receptors (Werhahn *et al.* 1999). In addition to inhibitory cortico-cortical circuits there are facilitatory pathways. One such circuit is termed intracortical facilitation (ICF) elicited by similar parameters to SICI, with a subthreshold CS, but at ISIs of 8–30 ms (Kujirai *et al.* 1993).

Motor cortex stimulation also inhibits the output of the contralateral motor cortex. This interhemispheric

inhibition (IHI) may be responsible for suppressing activity of the contralateral hemisphere to achieve hemispheric dominance while executing motor tasks. IHI can be measured by a paired pulse paradigm, a CS delivered to the contralateral motor cortex preceding the TS by 6–50 ms (Ferbert *et al.* 1992; Gerloff *et al.* 1998; Hanajima *et al.* 2001; Chen *et al.* 2003), or by the ipsilateral silent period (iSP) (Kujirai *et al.* 1993; Meyer *et al.* 1995; Trompetto *et al.* 2003), which refers to interruption of ongoing voluntary electromyographic (EMG) activity following stimulation of the ipsilateral motor cortex. IHIs at ISIs of 10 ms (IHI10) and 40 ms (IHI40) are probably mediated by different mechanisms (Chen *et al.* 2003). The neurotransmitter systems responsible for IHI have not been established, but IHI40 may be related to LICI (Kukaswadia *et al.* 2005), which is probably due to GABA_B mechanisms. Reductions in IHI10 have been demonstrated in several neurological and psychiatric disorders, such as schizophrenia (Daskalakis *et al.* 2002a), as well as in musicians who have trained from a young age (Ridding *et al.* 2000).

By characterizing the interactions between intracortical circuits and IHI, we can better understand the effects of abnormal intracortical circuits observed in disease states on activities of the contralateral hemisphere. Daskalakis *et al.* (2002b) studied how IHI interacts with intracortical circuits in the target hemisphere. It was found that IHI10 inhibits SICI and LICI reduces IHI10. Only one study examined how intracortical inhibitory circuits interact with transcallosal projections in the originating hemisphere. Trompetto *et al.* (2004) reported that SICI reduced the iSP area, suggesting that it suppresses the transcallosal motor output. However, the effects of SICI and ICF on IHI measured by the paired pulse method, and the effects of LICI have not been studied. We hypothesize that inhibitory and facilitatory circuits will produce widespread changes in the motor cortex, with similar effects on the cortico-spinal projections and the transcallosal projections.

Methods

Subjects

We studied 10 healthy volunteers (6 men and 4 women, mean age 35 years; range: 20–58 years). All subjects provided written informed consent. The experimental protocol was approved by the University Health Network Research Ethics Board in accordance with the *Declaration of Helsinki* on the use of human subjects in experiments.

EMG recording

Motor-evoked potentials (MEPs) were recorded by surface EMG from the left and right first dorsal interosseous (FDI) muscles using disposable disc electrodes in a belly tendon arrangement. The subjects in all experiments maintained relaxation and EMG activity was monitored using a computer screen and speakers at high gain. Trials with background muscle activity were rejected. When a constant contraction was required, the EMG passed through a leaky integrator and was displayed on an oscilloscope to provide visual feedback in addition to auditory feedback to the subject. The signal was amplified (Intronix Technologies, Bolton, Ontario, Canada), filtered (band-pass 2 Hz to 2.5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronics Design, Cambridge, UK), and stored in a laboratory computer for off-line analysis (Signal 3.07 software).

Transcranial magnetic stimulation setup

TMS was delivered to the left motor cortex using a figure-of-eight coil (mean diameter, 70 mm; maximum strength: 2.2 T) connected directly to a Magstim 200 stimulator (The Magstim Company, Dyfed, UK). The coil

was placed over the scalp area optimal for eliciting MEPs in the right FDI, with the handle pointing posteriorly, approximately perpendicular to the central sulcus and about 45 deg to the mid-sagittal line. This position was marked for reference. This orientation induced a posterior to anterior current (Werhahn *et al.* 1994).

TMS was delivered to the right motor cortex using a second figure-of-eight coil and four Magstim 200 stimulators connected to three BiStim Modules in a 'pyramid' arrangement. Each pair of Magstim 200 stimulators was connected to a BiStim Module and the output of the two BiStim Modules connected to a third BiStim Module that was connected to the TMS coil. This setup allowed the delivery of up to four pulses of different intensities to the right motor cortex at short intervals. This arrangement is associated with a power attenuation of about 15% (Sanger *et al.* 2001; Daskalakis *et al.* 2002b). The coil was placed over the scalp area optimal for eliciting MEPs in the left FDI. The coil orientation was the same as that for the left motor cortex.

To measure IHI, a suprathreshold contralateral CS (CCS) was delivered to the right motor cortex and a suprathreshold TS was delivered to the left motor cortex. ISIs of 10 ms (IHI10) and 40 ms (IHI40) were tested, as they represent different mechanisms (Chen *et al.* 2003). Both the CCS (right motor cortex) and the TS (left motor cortex) were set at the minimum intensity required to produce peak-to-peak MEP amplitude of 1 mV in five out of ten trials in the relaxed contralateral FDI muscle.

For the right motor cortex we tested different intracortical circuits (SICI, ICF, LICI) with paired pulses. CS were delivered 2, 10, or 100 ms prior to the CCS and are termed CS2, CS10, and CS100. CS2 was found to consistently produce SICI (Kujirai *et al.* 1993; Chen *et al.* 1998), and was set at an intensity of 95% of the active motor threshold (AMT). AMT was the lowest stimulator output required to produce MEPs of >200 μ V in five out of ten trials with a sustained contraction of 20% of maximal strength. CS10 was used to elicit ICF (Kujirai *et al.* 1993; Ridding *et al.* 1995b) and was also set at 95% AMT. CS2 and CS10 were set below the AMT to ensure that no descending corticospinal volleys were evoked (Nakamura *et al.* 1997; Di Lazzaro *et al.* 1998). CS100 was used to elicit LICI as it reduced cortical excitability (Chen *et al.* 1999) without affecting spinal excitability (Fuhr *et al.* 1991). It was set at the lowest intensity required to produce MEPs of 1 mV peak-to-peak amplitude in five out of ten trials with the muscle relaxed.

Experimental design

This study consisted of three experiments. The first experiment examined the effect of SICI on IHI, the second experiment tested the effect of ICF on IHI, and the third experiment tested the effect of LICI on IHI.

Table 1. Test conditions for experiment 1

Condition	Right motor cortex			Left motor cortex
	CS2	CCS10	CCS40	TS
1A				1 mV
1B		1 mV		1 mV
1C	95% AMT	1 mV		1 mV
1D	95% AMT			1 mV
1E		1mV _{CS2}		1 mV
1F	95% AMT	1mV _{CS2}		1 mV
1G			1 mV	1 mV
1H	95% AMT		1 mV	1 mV
1I	95% AMT			1 mV
1J			1mV _{CS2}	1 mV
1K	95% AMT		1mV _{CS2}	1 mV

Stimulus intensities. CS2, conditioning stimulus delivered 2 ms before the CCS to elicit SICI; CCS10, contralateral conditioning stimulus delivered 10 ms before the test stimulus (TS) to elicit IHI10; CCS40, contralateral conditioning stimulus delivered 40 ms before the TS to elicit IHI40. All the above stimuli were applied to the right motor cortex. TS, test stimulus applied to the left motor cortex to elicit an MEP in the right FDI. See Methods for CCS intensity nomenclature.

The CCS used to elicit IHI also served as the TS used to measure intracortical circuits in the right motor cortex. Thus, the ISIs for SICI, ICF, and LICI are in relation to the CCS. The CCS intensity needed to produce peak-to-peak MEP amplitudes of 1 mV is labelled 'CCS_{1mV}' and IHI produced by CCS of this intensity would be termed IHI_{1mV}. In some trials, we adjusted the CCS intensity to produce MEPs of ~1 mV in the presence of another inhibitory or facilitatory circuit, and these conditions were identified by subscripts. For example, a CCS of intensity 'CCS_{1mVCS2}' produced a 1 mV response in the presence of CS2 (SICI). IHI elicited by a CCS of this intensity would be termed IHI_{1mVCS2}.

If the same CCS intensities were used in the presence and absence of an inhibitory or excitatory circuit, MEP amplitudes in response to CCS would be different. This was a concern as IHI increases with increasing CS intensity and MEP amplitude (Chen *et al.* 2003). Since MEP amplitude and stimulus intensity could not be matched in the same trial, we designed the experiments to match the CCS stimulus intensity and CCS evoked MEP amplitude in the presence and absence of an inhibitory or excitatory circuit in different trials. To match for MEP amplitude, the CCS intensity was increased or decreased to produce a 1 mV MEP response in the presence of an inhibitory or facilitatory mechanism. We then compared IHI in the presence of intracortical inhibitory or facilitatory circuits elicited by this adjusted CCS to IHI elicited by a CCS that produced a 1 mV MEP response in the absence of inhibitory or facilitatory circuits. In stimulus intensity-matched trials, the CCS intensities were identical.

Experiment 1: effects of SICI on IHI

This experiment investigated the effects of SICI on IHI. It consisted of 11 conditions (1A–1K, Table 1) of 10 trials each delivered in a randomized order for a total of 110 trials. Conditions 1A to 1F examined the interaction between SICI and IHI10, while conditions 1G to 1K examined the interaction between SICI and IHI40. Since SICI reduces the amplitude of the CCS, which may affect the amount of IHI, the CCS intensity in conditions 1E, 1F, 1J, and 1K were increased to produce a 1 mV MEP response in the presence of a CS2 pulse. The resulting IHI was termed IHI_{1mVCS2} and allowed matching of the CCS MEP amplitude, resulting in similar degrees of cortico-spinal activation in the presence and absence of SICI. The effect of SICI on IHI was tested with three pulses in conditions 1C, 1F, 1H and 1K. Conditions 1B and 1G were used to determine the amount of IHI with a 1 mV CCS (IHI10_{1mV} and IHI40_{1mV}). Conditions 1E and 1J were used to determine the amount of IHI with the stronger CCS intensity (IHI10_{1mVCS2} and IHI40_{1mVCS2}). We compared IHI10 and IHI40 alone (IHI10: 1B/1A; IHI40: 1G/1A) to IHI10 and IHI40 in the presence of SICI (IHI10: 1F/1A; IHI40: 1K/1A) matched for MEP amplitude produced by the CCS pulse (~1 mV). We also compared IHI10 and IHI40 alone (IHI10: 1B/1A and 1E/1A; IHI40: 1G/1A and 1J/1A) to IHI10 and IHI40 in the presence of SICI matched for the stimulus intensity of the CCS pulse (IHI10: 1C/1A and 1F/1A; IHI40: 1H/1A and 1K/1A). The stimulus intensities of the CCS pulses were either 1 mV (IHI10: 1B/1A *versus* 1C/1A; IHI40 1G/1A *versus* 1H/1A) or CCS_{1mVCS2} (IHI10: 1E/1A *versus* 1F/1A; IHI40: 1J/1A

Table 2. Test conditions for experiment 2

Condition	Right motor cortex			Left motor cortex
	CS10	CCS10	CCS40	TS
2A				1 mV
2B		1 mV		1 mV
2C	95% AMT	1 mV		1 mV
2D	95% AMT			1 mV
2E		1mV _{CS10}		1 mV
2F	95% AMT	1mV _{CS10}		1 mV
2G			1 mV	1 mV
2H	95% AMT		1 mV	1 mV
2I	95% AMT			1 mV
2J			1mV _{CS10}	1 mV
2K	95% AMT		1mV _{CS10}	1 mV

Stimulus intensities. CS10, conditioning stimulus delivered 10 ms before the CCS to elicit ICF; CCS10, contralateral conditioning stimulus delivered 10 ms before the TS to elicit IHI10; CCS40, contralateral conditioning stimulus delivered 40 ms before the TS to elicit IHI40. The above stimuli were delivered to the right motor cortex. TS, test stimulus applied to the left motor cortex to elicit an MEP in the right first dorsal interosseous (FDI). See Methods for CCS intensity nomenclature.

versus 1K/1A). To ensure the CS2 pulse was not eliciting IHI, it was paired with the IHI TS in the absence of a CCS10 (1D) or CCS40 (1I).

Experiment 2: effects of ICF on IHI

Eleven conditions were tested as detailed in Table 2 (2A–2K). Ten trials of each condition were implemented in a randomized order, totalling 110 trials. Conditions 2A to 2F examined the interaction between ICF and IHI10, while conditions 2G to 2K examined the interaction between ICF and IHI40. The CCS intensities in conditions 2E, 2F, 2J, and 2K were decreased to produce a 1 mV MEP response in the presence of a CS10 pulse. The resulting IHI was termed IHI_{1mVCS10} and allowed matching of the CCS MEP amplitude resulting in similar degrees of corticospinal activation in the presence and absence of ICF. The effect of ICF on IHI was tested with three pulses in conditions 2C, 2F, 2H and 2K. Conditions 2B and 2G were used to determine the amount of IHI with a 1 mV CCS (IHI10_{1mV} and IHI40_{1mV}). Conditions 2E and 2J were used to determine the amount of IHI with the weaker CCS intensity (IHI10_{1mVCS10} and IHI40_{1mVCS10}). We compared IHI10 and IHI40 alone (IHI10: 2B/2A; IHI40: 2G/2A) to IHI10 and IHI40 in the presence of ICF (IHI10: 2F/2A; IHI40: 2K/2A) matched for MEP amplitude produced by the CCS pulse (~1 mV). We also compared IHI10 and IHI40 alone (IHI10: 2B/2A and 2E/2A; IHI40: 2G/2A and 2J/2A) to IHI10 and IHI40 in the presence of ICF matched for the stimulus intensity of the CCS pulse (IHI 10: 2C/2A and 2F/2A; IHI40: 2H/2A and 2K/2A). The stimulus intensities of the CCS pulses were either 1 mV (IHI10: 2B/2A *versus* 2C/2A; IHI40 2G/2A

versus 2H/2A) or 1mVCS10 (IHI10: 2E/2A *versus* 2F/2A; IHI40: 2J/2A *versus* 2K/2A). To ensure the CS10 pulse was not eliciting IHI, it was paired with the IHI TS in the absence of a CCS10 (2D) or CCS40 (2I).

Experiment 3: effects of LICI on IHI

Eleven conditions were tested as detailed in Table 3 (3A–3K). Ten trials of each condition were implemented in a randomized order, totalling 110 trials. Conditions 3A to 3F looked at the interaction between LICI and IHI10, while conditions 3G to 3K looked at the interaction between LICI and IHI40. In conditions 3E, 3F, 3J, and 3K, the CCS pulse was increased to produce a 1 mV MEP response in the presence of a CS100 pulse. The resulting IHI was termed IHI_{1mVCS100} and allowed matching of the CCS MEP amplitude, resulting in similar degrees of corticospinal activation in the presence and absence of LICI. The effect of LICI on IHI was tested with three pulses in conditions 3C, 3F, 3H and 3K. Conditions 3B and 3G were used to determine the amount of IHI with a 1 mV CCS (IHI10_{1mV} and IHI40_{1mV}). Conditions 3E and 3J were used to determine the amount of IHI with the stronger CCS intensity (IHI10_{1mVCS100} and IHI40_{1mVCS100}). We compared IHI10 and IHI40 alone (IHI10: 3B/3A; IHI40: 3G/3A) to IHI10 and IHI40 in the presence of LICI (IHI10: 3F/3A; IHI40: 3K/3A) matched for MEP amplitude produced by the CCS pulse (~1 mV). We also compared IHI10 and IHI40 alone (IHI10: 3B/3A and 3E/3A; IHI40: 3G/3A and 3J/3A) to IHI10 and IHI40 in the presence of LICI matched for the stimulus intensity of the CCS pulse (IHI 10: 3C/3A and 3F/3A; IHI40: 3H/3A and 3K/3A). The stimulus intensities of the CCS

Table 3. Test conditions for experiment 3

Condition	Right motor cortex			Left motor cortex
	CS100	CCS10	CCS40	TS
3A				1 mV
3B		1 mV		1 mV
3C	1 mV	1 mV		1 mV
3D	1 mV			1 mV
3E		1mV _{CS100}		1 mV
3F	1 mV	1mV _{CS100}		1 mV
3G			1 mV	1 mV
3H	1 mV		1 mV	1 mV
3I	1 mV			1 mV
3J			1mV _{CS100}	1 mV
3K	1 mV		1mV _{CS100}	1 mV

Stimulus intensities. CS100, conditioning stimulus delivered 100 ms before the CCS to elicit LICI; CCS10, contralateral conditioning stimulus delivered 10 ms before the TS to elicit IHI10; CCS40, contralateral conditioning stimulus delivered 40 ms before the TS to elicit IHI40. These stimuli were delivered to the right motor cortex. TS, test stimulus applied to the left motor cortex to elicit a MEP in the right FDI. See Methods for CCS intensity nomenclature.

pulses were either 1 mV (IHI10: 3B/3A versus 3C/3A; IHI40 3G/3A versus 3H/3A) or CCS_{1mVCS100} (IHI10: 3E/3A versus 3F/3A; IHI40: 3J/3A versus 3K/3A). To determine whether the CS100 pulse elicited IHI, it was paired with the IHI TS in the absence of a CCS10 (3D) or CCS40 (3I).

Data analysis

The peak-to-peak MEP amplitude for each trial was measured offline. MEP amplitudes were expressed as a ratio of the mean unconditioned MEP amplitude (condition A) for each subject. Ratios below one represent inhibition and ratios above one represent facilitation. Values are expressed as the mean \pm standard deviation (s.d.).

For experiment 1, the effect of SICI on IHI was determined by repeated-measures ANOVA with test condition for IHI as the repeated measure (IHI alone elicited by CCS of 1 mV, IHI alone elicited by CCS adjusted to produce a 1 mV MEP in the presence of SICI, IHI elicited by the adjusted CCS in the presence of SICI tested through the triple pulse configuration) and ISI for IHI (IHI10 and IHI40) as an independent variable. If the main effect was significant, Fisher's protected least significant difference (PLSD) *post hoc* test was used. In experiments 2 (effects of ICF on IHI) and 3 (effects of LICI on IHI), similar repeated-measures ANOVA and Fisher's PLSD *post hoc* test were used. For experiments 1 and 3, correlation between the strength of SICI and LICI to the change in IHI was tested using Pearson product-moment correlation coefficients. The threshold for significance was set at $P < 0.05$.

Results

Experiment 1: effects of SICI on IHI

All 10 subjects participated in this experiment. The TS delivered to the left motor cortex was set at $44.6 \pm 5.2\%$ of the stimulator output to produce a 1 mV MEP response in the right FDI. The mean TS MEP amplitude in the right FDI was 1.34 ± 0.4 mV (Table 1: condition 1A), which was reduced to 0.80 ± 0.4 mV by IHI10_{1mV} (condition 1B) and to 0.56 ± 0.4 mV by IHI40_{1mV} (condition 1G). With the stronger CCS pulse (denoted CCS_{1mVCS2}), the resulting inhibition was greater with IHI10_{1mVCS2} producing a 0.50 ± 0.4 mV response (condition 1E) and IHI40_{1mVCS2} producing a 0.41 ± 0.3 mV response (condition 1J).

IHI10 and IHI40 were elicited by CCS at $63.1 \pm 11.3\%$ of the stimulator output to produce a 1 mV MEP response in the left FDI and $79.1 \pm 16.7\%$ of the stimulator output to produce a 1 mV MEP response in the presence of SICI. The mean CCS_{1mV} MEP amplitude in the left FDI was 1.0 ± 0.2 mV (conditions 1B and 1G) and increased to 2.3 ± 1.1 mV with the stronger CCS_{1mVCS2} pulse (conditions 1E and 1J). CS2 at $42.3 \pm 8.8\%$ of stimulator output elicited SICI which reduced the MEP produced by the CCS_{1mV} pulse to 0.5 ± 0.3 mV (conditions 1C and 1H) and the CCS_{1mVCS2} pulse to 1.0 ± 0.3 mV (conditions 1F and 1K). Therefore, conditions 1B and 1F and conditions 1G and 1K were matched for MEP amplitude in the left FDI muscle.

Figure 1 illustrates the interaction between SICI and IHI40 in a representative subject. The CCS40 pulse elicited IHI40 that reduced the MEP amplitude evoked by the TS (Fig. 1A and B) in the right FDI muscle. With the addition of a CS2 pulse to produce SICI, the MEP elicited

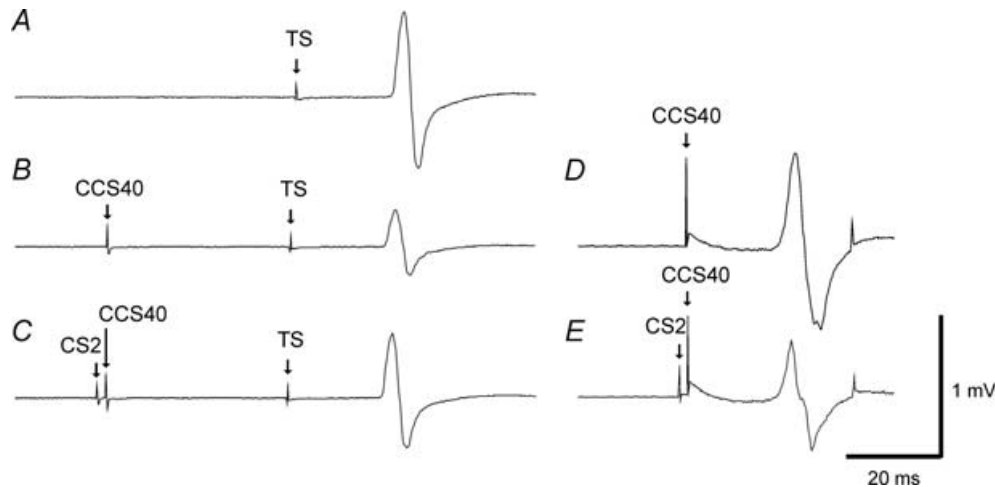


Figure 1. Effects of SICI on IHI40 in a representative subject

Each trace represents the average of 10 trials. Traces *A*, *B* and *C* are recordings from the right FDI muscle and traces *D* and *E* are concurrent recordings from the left FDI muscle. *A*, response to 1 mV TS alone (condition 1A). *B*, IHI40_{1mVCS2} alone: the adjusted CCS40_{1mVCS2} pulse inhibited the TS MEP (condition 1J). *C*, IHI40_{1mVCS2} in the presence of SICI: the CS2 pulse preceding the CCS40_{1mVCS2} pulse led to reduction of IHI as shown here by an increase in MEP amplitude (condition 1K). The presence of SICI was confirmed by a decrease in the MEP amplitude in the left FDI from *D* (condition 1J) to *E* (condition 1K), due to the CS2 pulse.

by the CCS40 pulse in the left FDI muscle was decreased (Fig 1*D* and *E*) as expected. However, the addition of the CS2 pulse increased the MEP amplitude in the right FDI muscle when matched for stimulus intensity (Fig. 1*B* and *C*). The grouped data for IHI_{1mV} (1B/1A, 1G/1A), IHI_{1mVCS2} (1E/1A, 1J/1A), and IHI_{1mVCS2} in the presence of SICI (1F/1A, 1K/1A) for IHI10 and IHI40 are shown in

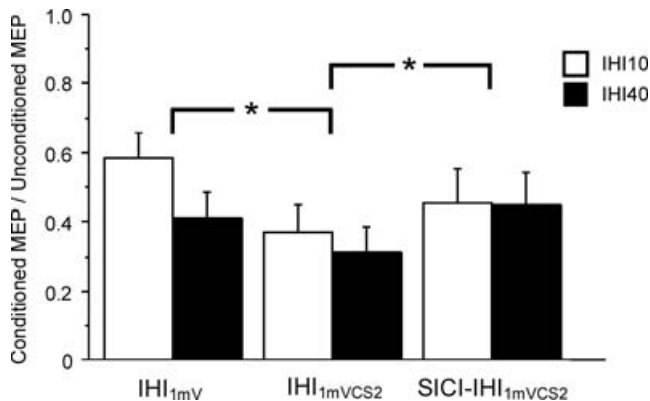


Figure 2. Effects of SICI on IHI10 and IHI40 data from 10 subjects IHI_{1mV} represents IHI with a CCS of 1 mV (IHI10: condition 1B/1A, IHI40: condition 1G/1A). IHI_{1mVCS2} represents IHI with intensity of the CCS adjusted to produce a 1 mV MEP in the left FDI muscle if preceded by a CS2 pulse (IHI10: condition 1E/1A, IHI40: condition 1J/1A). SICI-IHI_{1mVCS2} is IHI in the presence of SICI (IHI10: condition 1F/1A, IHI40: condition 1K/1A). SICI significantly reduced both IHI10 and IHI40 when matched for stimulus intensity (IHI_{1mVCS2} versus SICI-IHI_{1mVCS2}), but not when matched for MEP amplitude (IHI_{1mV} versus SICI-IHI_{1mVCS2}). Inhibition or facilitation is expressed as a ratio of the conditioned to unconditioned MEPs. Ratios above 1 represent facilitation and ratios below 1 represent inhibition. Error bars represent s.e.m. *Significant difference ($P < 0.05$).

Fig. 2 and Table 4. Repeated measures ANOVA indicated a significant effect of test conditions ($P = 0.0005$) but no significant effect of ISI (10 or 40 ms) on IHI. The test condition–ISI interaction was not significant. *Post hoc* tests revealed that the reduction in IHI10 and IHI40 by SICI was significant when matched for stimulus intensity ($P = 0.0056$) (Fig. 2, second and third column) but not when matched for MEP amplitude (Fig. 2, first and third column). In the other stimulus intensity-matched conditions, 1G and 1H (not shown in Fig. 2), the inhibition of IHI40 by SICI approached significance ($P = 0.067$). IHI elicited using the stronger CCS_{1mVCS2} pulse resulted in significantly greater inhibition of the test MEP (Fig. 2, first and second column, *post hoc* test, $P = 0.0001$). The CS2 pulse alone in conditions 1D and 1I did not produce IHI: the MEP ratios were 1.02 ± 0.06 for 1D/1A and 0.96 ± 0.09 for 1I/1A. The strength of IHI10 and IHI40 inhibition by SICI (1C/1A–1B/1A, 1H/1A–1G/1A) did not correlate with the strength of SICI (left FDI, 1C/1B or 1H/1G) when the CCS were matched for stimulus intensity ($r = 0.33$, $P = 0.35$). Similarly, no correlation ($r = 0.28$, $P = 0.24$) was found for conditions matched for the higher CCS intensity (IHI10: 1F/1A–1E/1A versus 1F/1E, IHI40: 1K/1A–1J/1A versus 1K/1J).

Experiment 2: effects of ICF on IHI

Nine subjects participated in this experiment as ICF could not be elicited in one subject. A TS of intensity $45.8 \pm 7.3\%$ of the stimulator output was delivered to the left motor cortex to produce TS MEP amplitude of 1.1 ± 0.4 mV in the right FDI (Table 2: condition 2A),

Table 4. Values for SICI, ICF, LICI and IHI10, IHI40 in experiments 1–3

Expt	IHI ISI	Left FDI			Right FDI			
		SICI	ICF	LICI	IHI	CS-IHI	IHI (adjusted CCS)	CS-IHI (adjusted CCS)
1	10	49 ± 17 (1C/1B, 1H/1G)	—	—	58 ± 22 (1B/1A)	65 ± 29 (1C/1A)	37 ± 25 (1E/1A)	45 ± 32 (1F/1A)
	40	—	—	—	41 ± 24 (1G/1A)	51 ± 29 (1H/1A)	31 ± 22 (1J/1A)	45 ± 31 (1K/1A)
2	10	—	158 ± 49 (2C/2B, 2H/2G)	—	56 ± 21 (2B/2A)	54 ± 22 (2C/2A)	68 ± 24 (2E/2A)	69 ± 19 (2F/2A)
	40	—	—	—	53 ± 25 (2G/2A)	59 ± 27 (2H/2A)	68 ± 27 (2J/2A)	71 ± 26 (2K/2A)
3	10	—	—	29 ± 12 (3C/3B, 3H/3G)	52 ± 23 (3B/3A)	86 ± 53 (3C/3A)	33 ± 19 (3E/3A)	55 ± 44 (3F/3A)
	40	—	—	—	49 ± 19 (3G/3A)	73 ± 36 (3H/3A)	33 ± 19 (3J/3A)	60 ± 33 (3K/3A)

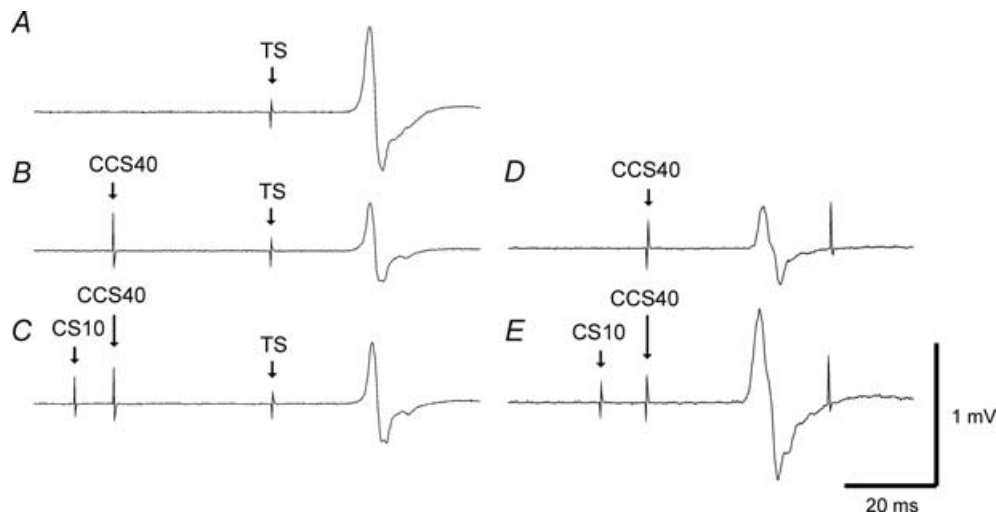
SICI, ICF, and LICI recorded from the left FDI muscle are expressed as percentages of the response to the CCS alone. IHI, recorded from the right FDI muscle, are expressed as percentages of the response to the test stimulus alone. IHI: elicited by CCS_{1mV}; CS-IHI: IHI_{1mV} in the presence of SICI, ICF, or LICI; IHI (adjusted CCS): elicited by a CCS adjusted to produce a 1 mV MEP response in the presence of intracortical inhibition or facilitation; CS-IHI (adjusted CCS): IHI_{1mVCS2} in the presence of SICI, IHI_{1mVCS10} in the presence of ICF, or IHI_{1mVCS100} in the presence of LICI. The corresponding conditions are listed in parentheses.

which decreased to 0.7 ± 0.4 mV due to IHI10_{1mV} (condition 2B) and 0.62 ± 0.4 mV due to IHI40_{1mV} (condition 2G). The weaker CCS pulse used to match for MEP amplitude (denoted CCS_{1mVCS10}) caused less inhibition with IHI10_{1mVCS10}, producing a 0.82 ± 0.4 mV response (condition 2E) and IHI40_{1mVCS10}, producing a 0.79 ± 0.4 mV response (condition 2J).

The mean CCS_{1mV} MEP amplitude in the left FDI was 1.3 ± 0.3 mV (conditions 2B and 2G, stimulus intensities $60.9 \pm 11.7\%$ of stimulator output) and decreased

to 0.9 ± 0.5 mV with the weaker CCS_{1mVCS10} pulse (conditions 2E and 2J, stimulus intensities $56.2 \pm 9.9\%$ of stimulator output). CS10 elicited ICF as it increased the amplitude of the MEP response produced by the CCS_{1mV} to 1.9 ± 0.4 mV (conditions 2C and 2H) and the MEP evoked by the CCS_{1mVCS10} pulse to 1.2 ± 0.2 mV (conditions 2F and 2K). Conditions 2B and 2F, and conditions 2G and 2K, were matched for MEP amplitude.

The interaction between ICF and IHI40 in a representative subject is shown in Fig. 3. The CCS40 pulse

**Figure 3. Effects of ICF on IHI40 in a representative subject**

Traces represent the average of 10 trials. Traces A, B and C are from the right FDI muscle, and traces D and E are concurrent recordings from the left FDI muscle. A, 1 mV TS MEP response (condition 2A). B, IHI40_{1mVCS10} alone: the TS MEP was inhibited by the CCS40_{1mVCS10} pulse (condition 2J). C, IHI40_{1mVCS10} in the presence of ICF: the CS10 pulse preceding the CCS40_{1mVCS10} pulse had no effect on IHI and there was no significant change in MEP amplitude (condition 2K). The presence of ICF was confirmed by the increase in MEP amplitude from D (condition 2J) to E (condition 2K) due to the CS10 pulse.

produced IHI40, which decreased the TS MEP amplitude (Fig. 3A and B). Addition of a CS10 pulse that preceded both CCS40 had no effect on TS MEP amplitude when conditions were matched for stimulus intensity (Fig. 3B and C), although the CS10 pulse led to ICF in the left FDI muscle (Fig. 3D and E). The data for all nine subjects for IHI_{1mV} (2B/2A, 2G/2A), IHI_{1mVCS10} (2E/2A, 2J/2A), and IHI_{1mVCS10} in the presence of ICF (2F/2A, 2K/2A) for IHI10 and IHI40 are shown in Fig. 4 and Table 4. Repeated measures ANOVA demonstrated a significant effect of test condition on IHI10 and IHI40 ($P = 0.0009$) but no significant effect of ISI. The test condition–ISI interaction was not significant. *Post hoc* tests revealed that ICF significantly reduced IHI10 and IHI40 when matched for MEP amplitude (Fig. 4, first and third column, $P = 0.0006$) but had no effect when matched for stimulus intensity (Fig. 4, second and third column). IHI elicited with the weaker CCS_{1mVCS10} resulted in significantly less inhibition (Fig. 4, first and second column, $P = 0.0017$). The CS10 pulse alone did not elicit any IHI (MEP ratios were 1.05 ± 0.01 for 2D/2A and 1.01 ± 0.01 for 2I/2A).

Experiment 3: effects of LICI on IHI

This experiment was conducted on nine subjects as IHI could not be elicited in one subject. A TS of

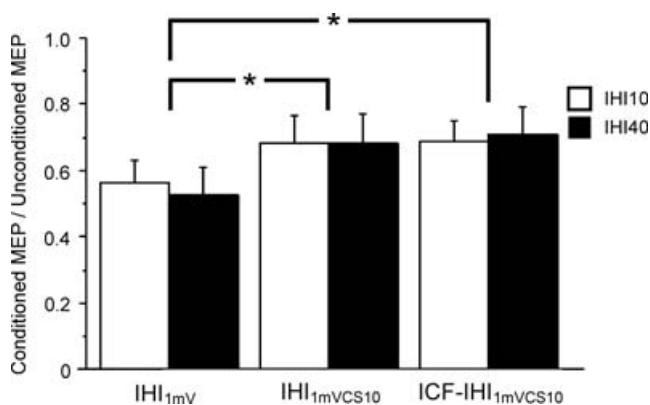


Figure 4. Effects of ICF on IHI10 and IHI40 data from nine subjects

IHI_{1mV} represents IHI with a CCS of 1 mV (IHI10: condition 2B/2A, IHI40: condition 2G/2A). IHI_{1mVCS10} represents IHI with intensity of the CCS adjusted to produce a 1 mV MEP in the left FDI if preceded by a CS10 pulse (IHI10: condition 2E/2A, IHI40: condition 2J/2A). ICF-IHI_{1mVCS10} is IHI in the presence of ICF (IHI10: condition 2F/2A, IHI40: condition 2K/2A). Both IHI10 and IHI40 were significantly reduced by ICF when matched for MEP amplitude (IHI_{1mV} versus ICF-IHI_{1mVCS10}), but not when matched for stimulus intensity (IHI_{1mVCS10} versus ICF-IHI_{1mVCS10}). Inhibition or facilitation is expressed as a ratio of the conditioned to unconditioned MEPs. Ratios above 1 represent facilitation and ratios below 1 represent inhibition. Error bars represent s.e.m. *Significant difference ($P < 0.05$).

intensity $44.9 \pm 7.3\%$ of the stimulator output was delivered to the left motor cortex to produce TS MEP amplitude of 1.14 ± 0.3 mV in the right FDI (Table 3: condition 3A), which was reduced to 0.71 ± 0.5 mV by IHI10_{1mV} (condition 3B) and 0.72 ± 0.6 mV by IHI40_{1mV} (condition 3G). With the stronger CCS pulse used to match for MEP amplitude (denoted CCS_{1mVCS100}), the resulting inhibition was greater for IHI10_{1mVCS100} producing a 0.53 ± 0.7 mV response (condition 3E) and IHI40_{1mVCS100} producing a 0.52 ± 0.5 mV response (condition 3J).

The mean MEP amplitude in the left FDI evoked by the CCS_{1mV} pulse was 1.2 ± 0.3 mV (conditions 3B and 3G, $60.7 \pm 11.6\%$ stimulator output) which increased to 2.6 ± 0.9 mV (conditions 3E and 3J, $74.4 \pm 16.8\%$ stimulator output) with the stronger CCS_{1mVCS100} pulse. LICI is demonstrated by reduction in the MEP amplitude produced by the CCS_{1mV} pulse to 0.2 ± 0.2 mV (conditions 3C and 3H) and the CCS_{1mVCS100} pulse to 1.1 ± 0.3 mV (conditions 3F and 3K) in the presence of CS100. Thus, conditions 3B and 3F and conditions 3G and 3K were matched for MEP amplitude.

Figure 5 illustrates the interaction between LICI and IHI40 in a representative subject. The CCS40 pulse elicited IHI40 that reduced the MEP amplitude evoked by the TS (Fig. 5A and B). Addition of the CS100 pulse increased the MEP amplitude in the right FDI muscle when matched for stimulus intensity (Fig. 5B and C). As expected, the CS100 pulse produced LICI, which decreased the MEP elicited by the CCS40 pulse in the left FDI muscle. Grouped data from all subjects for IHI_{1mV} (3B/3A, 3G/3A), IHI_{1mVCS100} (3E/3A, 3J/3A), and IHI_{1mVCS100} in the presence of LICI (3F/3A, 3K/3A) for IHI10 and IHI40 are shown in Fig. 6 and Table 4. Repeated measures ANOVA indicated a significant effect of test conditions ($P = 0.0012$) but no significant effect of ISI (10 or 40 ms) on IHI. The test condition–ISI interaction was not significant. *Post hoc* tests revealed that the reduction in IHI10 and IHI40 by LICI was significant when matched for stimulus intensity ($P = 0.0004$) (Fig. 6, second and third column) but not when matched for MEP amplitude (Fig. 6, first and third column). For conditions 3G and 3H that are also matched for test stimulus intensity (not shown in Fig. 6), the inhibition of IHI40 by LICI was also significant ($P = 0.03$). IHI elicited by the stronger CCS_{1mVCS100} produced significantly greater inhibition (Fig. 6, first and second column, $P = 0.0074$). The CS100 pulse alone in conditions 3D and 3I did not produce any IHI (MEP ratios 1.13 ± 0.09 for 3D/3A and 1.02 ± 0.1 for 3I/3A). The magnitude of IHI10 and IHI40 inhibition by LICI (3C/3A–3B/3A, 3H/3A–3G/3A) did not correlate with the strength of LICI (left FDI, 3C/3B or 3H/3G) when the CCS were matched for stimulus intensity ($r = 0.07$, $P = 0.79$). Similarly, no correlation ($r = 0.09$, $P = 0.74$) was found for conditions matched for the higher CCS intensity (IHI10: 3F/3A–3E/3A versus 3F/3E, IHI40: 3K/3A–3J/3A versus 3K/3J).

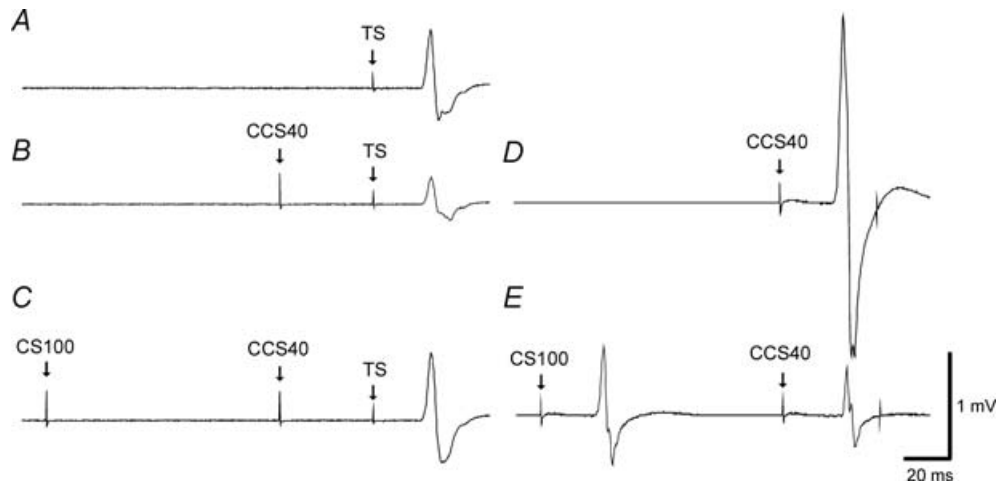


Figure 5. Effects of LICI on IHI40 in a representative subject

Waveforms are the average of 10 trials. Traces *A*, *B* and *C* are from the right FDI muscle and traces *D* and *E* are concurrent recordings from the left FDI muscle. *A*, response to 1 mV TS alone (condition 3A). *B*, IHI40_{1mVCS100} alone: the CCS40_{1mVCS100} pulse reduced the amplitude of the TS MEP (condition 3J). *C*, IHI40_{1mVCS100} in the presence of LICI: the CS100 pulse preceding the CCS40_{1mVCS100} pulse led to inhibition of IHI resulting in an increase in MEP amplitude (condition 3K). The presence of LICI in the left FDI muscle was demonstrated by reduction in the MEP amplitude from *D* (condition 3J) to *E* (condition 3K), due to the CS100 pulse.

Discussion

SICI and LICI inhibit IHI

Several observations suggest that IHI is mainly mediated by transcallosal fibres, although subcortical circuits may also contribute (Gerloff *et al.* 1998). IHI at short ISIs of about 10 ms are consistent with transcallosal conduction times (Ferbert *et al.* 1992). A CCS applied to one motor cortex reduced the size of descending corticospinal volleys from the contralateral motor cortex (Di Lazzaro *et al.* 1999) but did not attenuate the TS response evoked by an anodal electrical stimulus (Ferbert *et al.* 1992). This interhemispheric inhibition is probably transmitted through the corpus callosum (Meyer *et al.* 1995; 1998; Hoppner *et al.* 1999). Since GABAergic neurons are predominantly found in local circuits (Somogyi *et al.* 1998), it is likely that IHI is due to excitatory transcallosal fibres from the originating hemisphere that synapse to inhibitory interneurons in the target hemisphere to attenuate descending corticospinal output.

We found that both SICI and LICI significantly reduced IHI10 and IHI40 when matched for CCS intensity. It is likely that the CS2 and CS100 pulses inhibited the effects of the CCS pulse through reduced activation of transcallosal fibres that mediate IHI (Ferbert *et al.* 1992; Meyer *et al.* 1998). In the MEP amplitude (left FDI muscle) matched conditions, SICI or LICI produced no change in either IHI10 or IHI40. By increasing the intensity of the CCS pulse to match for a similar degree of corticospinal activation, the inhibitory influence of a preceding CS2 or CS100 was also compensated for, and produced similar degrees of transcallosal fibre activation as the CCS_{1mV} pulse alone. Therefore, SICI and LICI produced similar degrees

of inhibition for the corticospinal and transcallosal output systems.

It has been reported that SICI reduces iSP area (Trompetto *et al.* 2004). The similar effect of SICI on iSP and IHI40 is consistent with the suggestion that they may be related (Chen *et al.* 2003). Since IHI10 and IHI40 are mediated by different mechanisms (Chen *et al.* 2003),

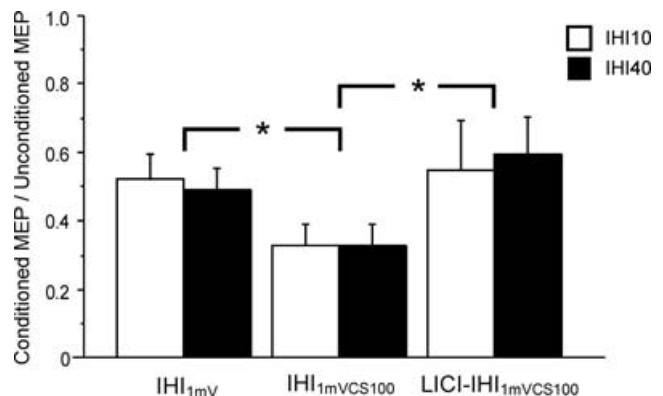


Figure 6. Effects of LICI on IHI10 and IHI40 data from nine subjects

IHI_{1mV} represents IHI with a CCS of 1 mV (IHI10: condition 3B/3A, IHI40: condition 3G/3A). IHI_{1mVCS100} represents IHI with intensity of the CCS adjusted to produce a 1 mV MEP in the left FDI muscle if preceded by a CS100 pulse (IHI10: condition 3E/3A, IHI40: condition 3J/3A). LICI-IHI_{1mVCS100} is IHI in the presence of LICI (IHI10: condition 3F/3A, IHI40: condition 3K/3A). LICI significantly reduced both IHI10 and IHI40 when matched for stimulus intensity (IHI_{1mVCS100} versus LICI-IHI_{1mVCS100}), but not when matched for MEP amplitude (IHI_{1mV} versus LICI-IHI_{1mVCS100}). Inhibition or facilitation is expressed as a ratio of the conditioned to unconditioned MEPs. Ratios above 1 represent facilitation and ratios below 1 represent inhibition. Error bars represent s.e.m. *Significant difference ($P < 0.05$).

both SICI and LICI appear to produce widespread cortical inhibition affecting several transcallosal circuits as well as the corticospinal output system.

The interactions between SICI and IHI10 are different for the originating hemisphere for IHI examined in this study compared to the target (contralateral) hemisphere, where IHI10 was found to inhibit SICI (Daskalakis *et al.* 2002b). However, LICI appears to inhibit IHI10 in both the originating and target hemispheres (Daskalakis *et al.* 2002b). The interactions between SICI, LICI and IHI40 in the target hemisphere have not been studied.

No interaction between ICF and IHI

In contrast to SICI and LICI, ICF had no effect on IHI10 and IHI40 when matched for the intensity of the CCS pulse. Although ICF reduced IHI10 and IHI40 when matched for MEP amplitude (Figs 3 and 4), this is probably because the CCS intensity was reduced in these trials to account for the facilitatory effect of ICF on MEP amplitude, and this resulted in reduced activation of the inhibitory transcallosal mechanism. These findings suggest that ICF does not interact with either IHI10 or IHI40, as the degree of IHI was solely contingent on the intensity of the CCS pulse irrespective of the presence of ICF. In the target hemisphere, a previous study also found no interaction between ICF and IHI10 (Daskalakis *et al.* 2002b).

This is consistent with the work of Trompetto *et al.* (2004) who found no change in iSP with ICF, although only three subjects were tested. The mechanisms underlying ICF remains unclear. Epidural recordings found no increase in the amplitude of descending corticospinal volleys associated with ICF, although MEP amplitudes

were increased (Di Lazzaro *et al.* 2006). However, there was also no evidence for changes in spinal excitability to account for ICF (Ziemann *et al.* 1996b; Di Lazzaro *et al.* 2006). If ICF is a cortical phenomenon, its influence is much more focused compared to SICI and LICI.

Different neuronal populations mediate IHI and corticospinal output

While it is known that corticospinal neurons originate from layer V of the cortex, the location of transcallosal neurons in the motor cortex remains controversial. Jacobson & Trojanowski (1974) used retrograde labelling and reported that cells of origin of the callosal system are found in layers II to VI, predominately in layers III and V. Casterman-Beerevoets *et al.* (1980) reported that retrogradely labelled callosal neurons are present in all layers except layer I. Jones *et al.* (1979) found that callosal projection cells arise from layer IIIB, but the study was conducted in the primary somatosensory cortex. By injecting retrograde tracers into the sensorimotor cortex and ipsilateral corticospinal tract at the C2 spinal segment of anaesthetized rats, Catsman-Berreoets *et al.* (1980) showed that the transcallosal fibres and the descending corticospinal tract are of different origin as there were no double-retrogradely labelled neurons in layer V of the non-injected hemisphere. They also found that layer V neurons of the sensorimotor cortex which responded to antidromic stimulation of the corticospinal tract could not be activated by antidromic stimulation of the corpus callosum. Thus, these animal studies suggest that transcallosal and corticospinal projecting cells are distinct.

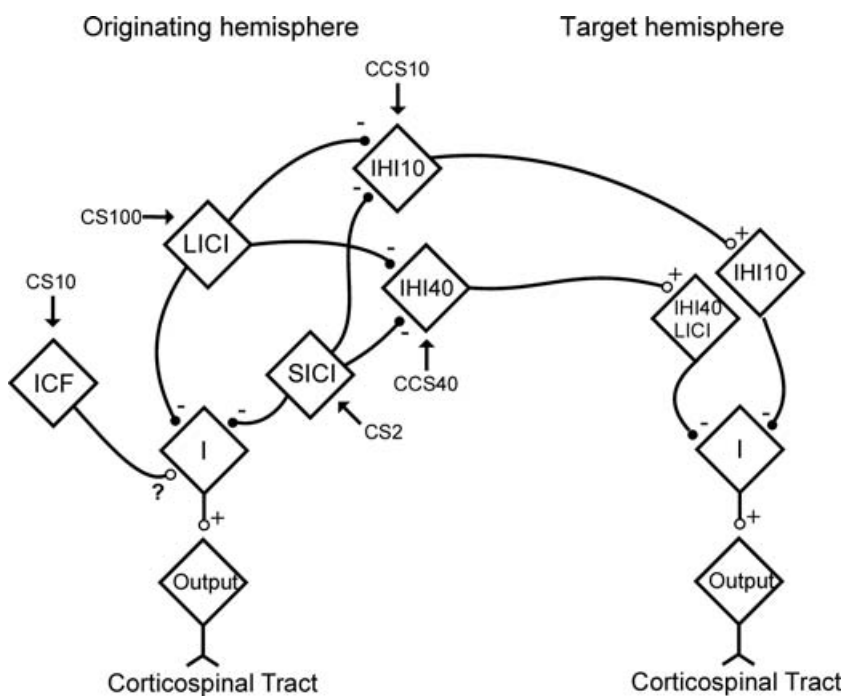


Figure 7. Model of interactions between intracortical and interhemispheric circuits

The diamonds represent neuronal circuits mediating SICI, LICI, ICF, IHI10 and IHI40. Arrows point to the circuits which the corresponding pulse activates. Excitatory connections are labelled by + and ○, while inhibitory connections are labelled by - and ●. The interaction between ICF and descending I-waves is labelled ?, as the mechanism underlying ICF has not been firmly established. In both the originating and target hemispheres for IHI, the 'I' diamond represents neurons that lead to descending I-waves, and the 'output' diamond represents corticospinal neurons. IHI10 and IHI40 are represented by different neuronal populations based on the results of previous studies (Chen *et al.* 2003; Kukawadia *et al.* 2005).

Two of our findings support the suggestion that the situation is similar in humans, that transcallosal fibres are not collaterals of corticospinal fibres, and transcallosal and corticospinal projection neurons belong to distinct populations. The first is that ICF facilitated the corticospinal output but had no effect on interhemispheric inhibition. The second is the lack of correlation between MEP inhibition and IHI inhibition by SICI and LICI. This is consistent with greater stimulus intensity required to produce iSP than MEPs (Trompetto *et al.* 2003), the suppression of iSP in subjects who failed to demonstrate SICI (Trompetto *et al.* 2004), and the different effects of the direction of induced currents on iSP and MEP latencies (Meyer *et al.* 1996).

A model of how intracortical inhibitory and facilitatory circuits interact with the corticospinal and transcallosal output systems that is consistent with the previous and the current observations is shown in Fig. 7. The corticospinal output and IHI are shown as mediated by different neuronal populations. IHI10 and IHI40 are also shown as due to different mechanisms, based on the results of previous studies (Chen *et al.* 2003; Kukaswadia *et al.* 2005). Both SICI and LICI inhibit IHI10 and IHI40, in addition to inhibition of the corticospinal output. However, ICF only affects the corticospinal output system and the question mark indicates that the nature of this interaction remains unclear (Di Lazzaro *et al.* 2006).

The IHI circuits probably send excitatory connections across the corpus callosum to activate inhibitory interneurons in the contralateral motor cortex. IHI10 and IHI40 are shown as separate in the target (contralateral) hemisphere, based on a previous study which also suggests that an overlapping population of interneurons mediate LICI and IHI40 (Kukaswadia *et al.* 2005).

Implications for findings in diseases

Disruptions in intracortical and transcallosal circuits are seen in various diseases, and our findings may provide a possible explanation for some of these observations. For example, reduction in SICI in the unaffected hemisphere (Shimizu *et al.* 2002; Butefisch *et al.* 2003) in stroke patients can potentially explain the increased IHI from the unaffected to the affected hemisphere before movement onset (Murase *et al.* 2004). In Parkinson's disease, decreased SICI (Ridding *et al.* 1995a) may be related to increased IHI in patients without mirror movements (Li *et al.* 2007). Our findings may also have implications in studies of plasticity and motor learning where there are changes in intracortical and transcallosal inhibition.

Conclusions

Separate neuronal populations give rise to transcallosal fibres and the descending corticospinal output. SICI and LICI generate diffuse cortical inhibition that affects both

the corticospinal output and transcallosal systems to a similar extent, whereas ICF influences only the corticospinal output system.

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