Impaired interhemispheric inhibition in writer's cramp

A.J. Nelson, PhD
T. Hoque, BSc
C. Gunraj, MSc
Z. Ni, PhD
R. Chen, MBBChir,
MSc, FRCPC

Address correspondence and
reprint requests to Dr. Robert
Chen, 7MC-411, Toronto
Western Hospital, 399 Bathurst
Street, Toronto, Ontario, M5T
2S8, Canada
robert.chen@uhn.on.ca

ABSTRACT

Objectives: Reduced cortical inhibition is a feature of focal hand dystonia and this likely contributes to excessive muscle contractions. Inhibition from the opposite hemisphere, known as interhemispheric inhibition (IHI), was studied bidirectionally in 7 right-handed patients with writer's cramp (WC) and age-matched healthy controls in a cross-sectional physiologic study.

Methods: IHI was measured with paired transcranial magnetic stimulation with the conditioning stimulus applied to the motor cortex and the test stimulus applied to the contralateral motor cortex. Surface EMG was measured in right and left first dorsal interosseous muscles during rest, and while holding a pen between the thumb and index finger at 20% maximum voluntary contraction with the right dystonia-affected hand. The time course and magnitude of IHI was studied at interstimulus intervals of 6, 8, 10, 12, 30, 40, and 50 msec between the conditioning stimulus and test stimulus.

Results: In WC at rest, IHI was significantly reduced in the dystonia-affected right hand (IHI from right to left motor cortex) at both short (SIHI, 10–12 msec) and long (LIHI, 30–40 msec) intervals compared to the unaffected hand. Compared to controls, SIHI and LIHI were reduced in the dystonia-affected hand only. There was no difference in IHI between controls and WC during the task of holding a pen.

Conclusions: In WC, both SIHI and LIHI are reduced in the dystonia-affected hand compared to the unaffected hand and to healthy controls. Impaired IHI may contribute to excessive muscle contraction in WC. *Neurology*® 2010;75:441–447

GLOSSARY

ANOVA = analysis of variance; **CS** = conditioning stimulus; **FDI** = first dorsal interosseous; **FHD** = focal hand dystonia; **GABA** = gamma-aminobutyric acid; **IHI** = interhemispheric inhibition; **ISI** = interstimulus interval; **LIHI** = long interhemispheric inhibition; **MEP** = motor evoked potential; **MVC** = maximum voluntary contraction; **SICI** = short-interval intracortical inhibition; **SIHI** = short interhemispheric inhibition; **TMS** = transcranial magnetic stimulation; **TS** = test stimulus; **WC** = writer's cramp.

Focal hand dystonia (FHD) is a movement disorder that impairs hand control during a well-rehearsed, specific task such as writing (writer's cramp [WC]) or playing a musical instrument. Although the origin of the disorder remains unclear, previous studies suggest that the primary motor cortex (M1) contralateral to the dystonia-affected hand is hyperexcitable and exhibits reduced cortical inhibition.^{1–8} A magnetic resonance spectroscopy study suggested that gamma-aminobutyric acid (GABA) concentrations in sensorimotor cortex are reduced.⁹

Interhemispheric interactions between homologous muscle representations in M1 are mediated by transcallosal connections.^{10,11} This interaction may be probed using paired-pulse transcranial magnetic stimulation (TMS) in humans. A conditioning stimulus (CS) is delivered to the muscle representation in one hemisphere followed by a test stimulus (TS) to the homologous area in the opposite hemisphere. Using this approach, a net inhibitory effect of one hemisphere upon the other is observed, an interaction coined interhemispheric inhibition (IHI). In FHD, the increased excit-

From the Division of Neurology and Krembil Neuroscience Centre (A.J.N., T.H., C.G., Z.N., R.C.), Toronto Western Research Institute, University of Toronto, Toronto; and Department of Kinesiology (A.J.N.), University of Waterloo, Waterloo, Canada.

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Table Patient demographics ^a					
Patient	Age, y	Gender	Writer's Cramp Rating Scale	Symptom duration, y	Diagnosis
1	38	F	9	15	Dystonic cramp
2	35	F	8	7	Simple writer's cramp
3	40	M	4	11	Simple writer's cramp
4	42	M	7	9	Simple writer's cramp
5	58	F	7	8	Dystonic cramp
6	63	M	6	11	Simple writer's cramp
7	32	M	3	4	Simple writer's cramp

^a Simple writer's cramp refers to dystonic symptoms occurring only during writing. Dystonic cramp indicates that dystonia also occurred with writing and other tasks. None of the patients had mirror dystonia.

ability in M1 contralateral to the dystonia-affected hand may result from a reduction in IHI received.

In the present study, IHI was tested bidirectionally in right-handed participants with WC and controls. The first aim was to charac-

terize the time course of IHI bidirectionally to test the hypothesis that, in WC, IHI is selectively reduced in the dystonia-affected hand at both short and long latencies. Second, we tested whether the task of holding a pen alters IHI in patients with WC compared to controls. We hypothesized that during the task of holding a pen, IHI will not be reduced in patients with WC as it is in healthy subjects.

METHODS Subjects. Seven patients with WC (mean age 44 years, range 32–63 years, 3 women; table) and 7 healthy controls (mean age 42 years, range 32–62 years, 3 women) were studied. Patients with WC were recruited from the Toronto Western Hospital Movement Disorders Clinic from April to July 2008. Right-handedness was confirmed at 100% for all participants using a subset of the Oldfield Handedness Inventory.¹² None of the patients demonstrated any mirror dystonia and they had not received botulinum toxin injections for at least 4 months prior to study. All participants provided written informed consent. The Writer's Cramp Rating Scale was used to assess symptom severity.¹³ The University Health Network Research Ethics Board approved the study.

EMG recording. Surface EMG was recorded from the first dorsal interosseous (FDI) muscles in the right and left hands with the active electrode placed over the muscle belly and referenced to the metacarpophalangeal joint of the index finger. EMG signals were amplified (1,000×), bandpass filtered (20 Hz to 2.5 kHz, Intrinix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), digitized at 5 kHz (Micro1401, Cambridge Electronics Design, Cambridge, UK), and stored in a computer for off-line analysis. The EMG from FDI contralateral to the TS coil was also passed through a leaky integrator and the EMG level was displayed on an oscilloscope (a bright line) and transmitted through a speaker for visual and auditory feedback. For part of the experiment, participants were required to match the line to a target line that marked their level of contraction for 20% maximum voluntary contraction (MVC). Twenty percent MVC was calculated prior to TMS. The left hand remained relaxed throughout the experiment.

Neuro-navigation and TMS techniques.Brainsight apparatus was used to hold the chin and forehead in place (Rogue Research, Canada). Fiducial markers were coregistered with MRI obtained on a 3-T GE scanner (172 images) with 3D FSPGR-IR sequences using a 20-cm field of view (256 × 256). TMS was delivered using 2 custom-built 60-mm-diameter figure-of-8 “branding iron” coils whereby the handle points perpendicular to the plane of the wings (Magstim Company, UK). The coils were connected to 2 Magstim 200 stimulators. Each coil was positioned over the scalp area optimal for eliciting motor evoked potentials (MEPs) in the contralateral FDI muscle (motor hotspot) at approximately 45° to the midsagittal line. Each coil was equipped with optical sensors and the location and orientation of both coils were registered with the MRI using Brainsight Neuronavigation for online verification of coil placement, orientation, and repositioning between subject breaks. The coils were securely held in position using coil holders. The motor hotspots for all participants were localized at the precentral gyrus.

The TMS intensities to evoke ~1 mV MEP in the right and left FDI muscles were determined at rest and at 20% MVC of

Figure 1 Background EMG areas

A Right to left IHI

B Left to right IHI

Prestimulus EMG area recorded from left and right first dorsal interosseous (FDI) during rest and active conditions. Note that pen hold is performed only with the right hand. (A) Data recorded during interhemispheric inhibition (IHI) measured in RFDI (conditioning stimulus [CS] to right M1, test stimulus [TS] to left M1). (B) Data recorded during IHI measured in LFDI (CS to left M1, TS to right M1). Background EMG does not differ significantly between groups and is greater only during the task of holding the pen. The left hand is at rest in both groups during the active task and during the rest condition. * $p < 0.05$. WC = writer's cramp.

the right FDI muscle. Interhemispheric interactions were investigated by delivering a CS to the FDI motor hotspot in one hemisphere followed by a TS to the FDI hotspot in the opposite hemisphere.¹⁴ In an 8-minute acquisition period, 7 CS-TS interstimulus intervals (ISI) and TS alone were presented randomly (6, 8, 10, 12, 30, 40, 50 msec) and each repeated 10 times. Each CS-TS pair occurred once every 5–6 seconds. Two conditions were tested: 1) rest, whereby both hands were completely relaxed as determined by online EMG recordings; and 2) pen hold in the right hand: isometric 20% MVC of the right FDI while holding a pen between the thumb and index finger with the pen tip in contact with paper. The 2 conditions were tested while CS was applied to the right M1 and TS applied to the left M1 to test the IHI from the nondominant to the dominant motor cortex, and while the CS was applied to left M1 and TS to right M1 to test the dominant to nondominant IHI. The order of IHI direction was randomized across participants. The intensity of both the CS and TS was adjusted to evoke a 1-mV MEP in contralateral FDI depending on whether the contralateral muscle was at rest or active. Specifically, when the hand contralateral to the TS pulse was at rest, the TMS intensity was adjusted to evoke a 1 mV MEP in that relaxed hand. When the hand contralateral to the TS pulse was active (i.e., pen hold), the TMS intensity was adjusted to evoke a 1 mV MEP in the active muscle. This consideration is important since the degrees of SIHI and LIHI are dependent

on the CS and TS intensities.^{14–16} Trials contaminated by EMG in the resting hand were rejected on and off-line.

Data analyses. The peak-to-peak MEP amplitude was measured off-line and the paired-pulse MEP amplitude was expressed as a ratio of the mean unconditioned MEP amplitude (TS alone) for each condition; ratios below 1 represent inhibition and ratios above 1 represent facilitation. The area of prestimulus EMG was calculated for an 18-msec window prior to the first TMS pulse for each trial. This measure was used to compare background EMG levels across rest and pen holding conditions to ensure that the left hand was relaxed at all times and that the right hand muscle activation was similar across patients and controls. The prestimulus EMG levels and TMS intensities used were tested separately using 2-way analysis of variance (ANOVA) with independent factor group and condition.

To test the hypothesis that SIHI and LIHI reduction is specific to the dystonia-affected hand in patients with WC, data from 10-msec and 12-msec ISI were averaged for SIHI and data from 30-msec and 40-msec ISI were averaged for LIHI. SIHI and LIHI for the affected and unaffected hands were compared using paired *t* tests with alpha set at $p < 0.05$ for a 1-tailed test.

To examine the time course of IHI between conditions and groups, 2 3-way repeated-measures ANOVAs were performed: 1 for IHI recorded in the dystonia-affected, right FDI and 1 for IHI recorded in left FDI. Independent factors included group (2 levels: WC, controls), condition (2 levels: rest, pen hold with the right hand), and ISI (7 levels: 6, 8, 10, 12, 30, 40, 50 msec) with condition and ISI as within-subject factors and group as a between-subject factor. Post hoc Tukey tests were used to identify significant interactions whereby significance was set at $p < 0.007$ to accommodate 7 comparisons (1 for each ISI).

RESULTS The TMS intensity to evoke 1 mV MEP from left M1 was lower during the active pen hold compared to rest for both groups (WC: $47.7 \pm 7.5\%$ of stimulator output in rest, $37.4 \pm 6.4\%$ in active, $p = 0.001$; controls: $42.7 \pm 3.0\%$ in rest, $38.8 \pm 3.8\%$ in active, $p = 0.04$) but there were no differences between groups during rest or active pen hold. Figure 1 shows the prestimulus EMG area during IHI testing in the right FDI (right to left IHI, figure 1A) and left FDI (left to right IHI, figure 1B) muscles. The prestimulus EMG area measured in right FDI is greater during the pen hold task compared to rest for IHI measured in both directions (right to left IHI, WC, $p = 0.006$, controls, $p = 0.007$; left to right IHI, WC, $p = 0.0032$, controls, $p = 0.0037$) and was similar across groups during all conditions. The left FDI muscle remained relaxed during activation of the right hand in the pen hold condition in both groups.

Bidirectional IHI during rest in WC. Figure 2A plots the group-averaged time course of IHI measured in the right FDI (dystonia-affected hand) and left FDI (unaffected hand) muscles during the rest condition in WC participants. Figure 2B displays the data for SIHI (10 and 12 msec) and LIHI (30 and 40 msec). Both SIHI (paired *t* test, $p = 0.041$) and LIHI (paired *t* test, $p = 0.034$) were reduced in the

Figure 2 Interhemispheric inhibition (IHI) in writer's cramp (WC) during rest

(A) Group-averaged motor evoked potential (MEP) amplitudes (with standard errors) recorded in the right, dystonia-affected hand (conditioning stimulus [CS] to right M1, test stimulus [TS] to left M1) and left, unaffected hand (CS to left M1, TS to right M1) during rest. (B) Group-averaged histograms comparing short interhemispheric inhibition (SIHI) (10–12 msec) and long interhemispheric inhibition (LIHI) (30–40 msec) in the right affected hand compared to the left unaffected hand. Both SIHI and LIHI are reduced in the dystonia-affected hand. * $p < 0.05$.

dystonia-affected hand compared to the unaffected left hand. In controls, SIHI (paired t test, $p = 0.24$) and LIHI (paired t test, $p = 0.15$) in the right vs left FDI muscles were not different. Unpaired t tests revealed reduction in SIHI ($p = 0.03$) and LIHI ($p = 0.01$) in WC compared to controls for the right FDI muscle but there were no group differences for SIHI or LIHI in the left FDI muscle. These findings suggest that the reduced SIHI and LIHI in the dystonia-affected hand were not due to hand dominance.

IHI measured in right hand (dystonia-affected hand). Three-way ANOVA revealed a main effect of ISI ($F_{6,72} = 3.93$, $p = 0.0019$) and an interaction between group, condition, and ISI ($F_{6,72} = 2.27$, $p = 0.046$). There were no main effects of group or condition, and the group by condition interaction was not significant ($p = 0.141$). Figure 3A plots the group data in WC vs controls during rest and figure 3B plots the data during

pen hold. During rest (figure 3A), IHI was significantly reduced at 8, 12, 40, and 50 msec in WC compared to controls. During the context of holding a pen with the right hand (figure 3B), the time course of IHI was similar for both groups.

IHI measured in left hand (unaffected hand). The 3-way ANOVA revealed main effects of condition (2 levels, $F_{1,12} = 10.78$, $p = 0.0065$) and ISI (7 levels, $F_{6,72} = 2.77$, $p = 0.017$) but not group, and there was no significant interaction between factors. The group data comparing WC and controls for the unaffected hand are shown in figure 4A for rest and figure 4B for pen hold. For both groups, the task of holding the pen in the right (dystonia-affected) hand significantly reduces IHI in the left hand compared to rest, with no differences between groups. IHI recorded from the unaffected hand is not different from controls during rest or during the task of holding a pen in the dystonia-affected hand.

Figure 3 Writer's cramp (WC) vs controls for right to left interhemispheric inhibition (IHI) measured in the right first dorsal interosseous muscle (dystonia-affected hand)

Group-averaged motor evoked potential (MEP) amplitudes (with standard error) during rest (A, top) and holding a pen with the right hand (B, bottom). At rest (A), IHI in the dystonia-affected hand was reduced at short and long interstimulus intervals compared to controls (8 msec, $p = 0.002$, 12 msec, $p < 0.0001$, 40 msec, $p < 0.0001$, 50 msec, $p = 0.006$). During pen hold (B) with the dystonia-affected hand, IHI is not significantly different from controls. TS = test stimulus.

DISCUSSION The present study used paired-pulse TMS to probe IHI in patients with WC during rest and during 20% MVC while holding a pen with the right, dystonia-affected hand. The data revealed a reduction in both SIHI and LIHI in the symptomatic right hand in patients with WC compared to controls during relaxation but not during the task of holding a pen. IHI in the asymptomatic left hand was not different from controls.

IHI can be divided into short and long phases¹⁷ with different physiologic properties.^{16,18} Pharmacologic studies suggest that LIHI is mediated by postsynaptic GABA type B ($GABA_B$) receptors since administration of $GABA_B$ agonist baclofen increased LIHI but not SIHI.¹⁹ The neurotransmitter or receptor mediating SIHI remains unknown.¹⁹ The reduction of SIHI and LIHI in the dystonia-affected hand is observed when the CS pulse is delivered to right M1 and the TS pulse is delivered to left M1, contralateral to the dystonic hand. At least 3 possibilities exist for the source of the deficit in IHI. First, there may be deficits in the transcallosal projecting neurons in the unaffected M1 since physiologic^{1,4} and structural imaging studies²⁰ demonstrated abnormalities in the M1 ipsilateral to the affected hand in WC. However, cortical inhibitory circuits such as short-interval intracortical inhibition (SICI) are reduced in the ipsilateral M1.^{1,4} Previous studies showed that cortical inhibitory circuits in the originating hemisphere of IHI reduces both SIHI and LIHI.²¹ A reduction in cortical inhibition in the ipsilateral M1 as seen in dystonia is expected to increase rather than decrease SIHI and LIHI, and therefore cannot account for our findings. Moreover, a

Figure 4 Writer's cramp (WC) vs controls for left to right interhemispheric inhibition (IHI) measured in the left first dorsal interosseous muscle

Group-averaged motor evoked potential (MEP) amplitudes (with standard errors) comparing WC vs controls during rest (A, top) and pen hold with the right hand (B, bottom). No significant differences between groups are observed for either task. TS = test stimulus.

voxel-based morphometry study found reduced gray matter in the affected left M1 but not the unaffected right M1.²² Therefore, we consider this possibility unlikely. Second, there may be impairment of transcallosal fibers causing abnormal IHI in WC. Diffusion-tensor imaging studies have found abnormal fractional anisotropy in the corpus callosum in primary segmental dystonia,^{23,24} although studies in patients with WC have not been reported. Fractional anisotropy in callosal motor fibers was found to correlate with the degree of SIHI in normal subjects.²⁵ Third, the transcallosal fibers activate the local inhibitory circuits on the affected side and these circuits may be impaired. Previous studies have consistently found impaired cortical inhibition in the affected left M1 in WC³⁻⁵ and a structural MRI study found decreased gray matter in the left M1 but not in the right M1 in WC.²²

We did not observe a reduction in IHI in the asymptomatic left hand. Transcallosal inhibition was reported to be increased in the unaffected hand, as measured by an increase in the ipsilateral silent period⁸ and physio-

logic abnormalities occurred on both the symptomatic and asymptomatic sides.^{1,4} Such findings may represent predisposing factors or “endophenotypes” that are not directly related to dystonic symptoms. Since reduced IHI was found on the symptomatic side only, this observation may be more directly related to dystonic symptoms. However, during pen hold with the right hand, IHI is reduced in the left hand for both controls and WC. This effect may relate to the change in the effectiveness of the conditioning pulse during contraction of the contralateral hand.

In patients with WC, IHI is diminished during pen hold compared to at rest, consistent with our previous study in healthy controls.²⁶ Although we hypothesized that IHI would not be reduced in patients with WC during the pen holding task, as it is in controls, this was not the case. It may be that the task chosen may have been insufficient to engage the neural circuits responsible for the maladaptive motor control since the pen holding without writing did not trigger dystonia in our patients. However, we did not study the task of actual writing since it would be difficult to match the degree of muscle contraction between WC and controls. The requirement imposed by the pen hold condition may set IHI to the similar levels required for movement execution in both dystonic patients and controls. On the other hand, in the rest condition there is no requirement to set the IHI to certain level and resting IHI may assume a “natural” state. One study found that patients with WC with mirror dystonia exhibited reduced SIHI compared to controls but only during the premovement phase but not during phasic or tonic contraction.²⁷ We did not study the premovement phase and we specifically excluded our patients with mirror dystonia to ensure that our findings are not related to mirror dystonia.

Reduced cortical inhibition during voluntary contraction may be required to allow ongoing muscle activity. However, IHI during pen hold was the same for WC and controls. One suggestion is that reduced IHI at rest is a compensatory mechanism for the dystonia-affected hand to allow for a faster increase in cortical excitability to the active level but a further increase in excitability is not required during the active state. Similar results for reduced cortical inhibition at rest but not at active state were found in other clinical settings such as amputation²⁸ and functioning muscle transfer.²⁹

Although the functional correlates of reduced IHI are yet unknown, reduced IHI may contribute to co-contraction of agonist and antagonist muscles, prolonged EMG bursts,³⁰ and overflow of muscle activities seen in WC. The finding that IHI is abnormal only on the affected side makes it more likely that it is related to dystonia symptoms than other

physiologic measures such as reduced SICI and cortical silent period that are present on both sides.^{1,4} It is possible that reduced IHI at rest is a compensatory mechanism for the dystonia-affected hand to allow for a faster increase in cortical excitability to the active level, but may contribute to excessive muscle contraction in tasks that induced dystonia. The findings also have implications for treatment of dystonia. For example, low-frequency repetitive TMS reduced SIHI and LIHI bidirectionally with the strongest reduction in unstimulated side.³¹ Patients with WC showed increased blood flow changes following low-frequency repetitive TMS³² and transient improvement was reported in patients with WC.³³ Therefore, the effects on IHI should be considered in the development of novel therapies for WC.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Aimee J. Nelson.

DISCLOSURE

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REFERENCES

- Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. The pathophysiology of primary dystonia. *Brain* 1998;121:1195–1212.
- Mavrouidakis N, Caroyer JM, Brunko E, Zegers dB. Abnormal motor evoked responses to transcranial magnetic stimulation in focal dystonia. *Neurology* 1995;45:1671–1677.
- Ikoma K, Samii A, Mercuri B, Wassermann EM, Hallett M. Abnormal cortical motor excitability in dystonia. *Neurology* 1996;46:1371–1376.
- Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. *J Neurol Neurosurg Psychiatry* 1995;59:493–498.
- Chen R, Wassermann EM, Canos M, Hallett M. Impaired inhibition in writer's cramp during voluntary muscle activation. *Neurology* 1997;49:1054–1059.
- Filipovic SR, Ljubisavljevic M, Svetel M, Milanovic S, Kacar A, Kostic VS. Impairment of cortical inhibition in writer's cramp as revealed by changes in electromyographic silent period after transcranial magnetic stimulation. *Neurosci Lett* 1997;222:167–170.
- Rona S, Berardelli A, Vacca L, Inghilleri M, Manfredi M. Alterations of motor cortical inhibition in patients with dystonia. *Mov Disord* 1998;13:118–124.
- Niehaus L, Alt-Stutterheim K, Roricht S, Meyer BU. Abnormal postexcitatory and interhemispheric motor cortex inhibition in writer's cramp. *J Neurol* 2001;248:51–56.
- Levy LM, Hallett M. Impaired brain GABA in focal dystonia. *Ann Neurol* 2002;51:93–101.
- Matsunami K, Hamada I. Effects of stimulation of corpus callosum on precentral neuron activity in the awake monkey. *J Neurophysiol* 1984;52:676–691.
- Gould HJ, III, Cusick CG, Pons TP, Kaas JH. The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. *J Comp Neurol* 1986;247:297–325.
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97–113.
- Wissel J, Kabus C, Wenzel R, et al. Botulinum toxin in writer's cramp: objective response evaluation in 31 patients. *J Neurol Neurosurg Psychiatry* 1996;61:172–175.
- Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. *J Physiol* 1992;453:525–546.
- Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R. The mechanisms of interhemispheric inhibition in the human motor cortex. *J Physiol* 2002;543:317–326.
- Kukawadia S, Wagle-Shukla A, Morgante F, Gunraj C, Chen R. Interactions between long latency afferent inhibition and interhemispheric inhibitions in the human motor cortex. *J Physiol* 2005;563:915–924.
- Ni Z, Gunraj C, Nelson A et al. Two phases of interhemispheric inhibition between motor related cortical areas and the primary motor cortex in human. *Cereb Cortex* 2009;19:1654–1665.
- Chen R, Yung D, Li JY. Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J Neurophysiol* 2003;89:1256–1264.
- Irlbacher K, Brocke J, Mechow JV, Brandt SA. Effects of GABA(A) and GABA(B) agonists on interhemispheric inhibition in man. *Clin Neurophysiol* 2007;118:308–316.
- Garraux G, Bauer A, Hanakawa T, Wu T, Kansaku K, Hallett M. Changes in brain anatomy in focal hand dystonia. *Ann Neurol* 2004;55:736–739.
- Lee H, Gunraj C, Chen R. The effects of inhibitory and facilitatory intracortical circuits on interhemispheric inhibition in the human motor cortex. *J Physiol* 2007;580:1021–1032.
- Delmaire C, Vidailhet M, Elbaz A, et al. Structural abnormalities in the cerebellum and sensorimotor circuit in writer's cramp. *Neurology* 2007;69:376–380.
- Colosimo C, Pantano P, Calistri V, Totaro P, Fabbrini G, Berardelli A. Diffusion tensor imaging in primary cervical dystonia. *J Neurol Neurosurg Psychiatry* 2005;76:1591–1593.
- Fabbrini G, Pantano P, Totaro P, et al. Diffusion tensor imaging in patients with primary cervical dystonia and in patients with blepharospasm. *Eur J Neurol* 2008;15:185–189.
- Wahl M, Lauterbach-Soon B, Hattingen E, et al. Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. *J Neurosci* 2007;27:12132–12138.

26. Nelson AJ, Hoque T, Gunraj C, Ni Z, Chen R. Bi-directional interhemispheric inhibition during unimanual sustained contractions. *BMC Neurosci* 2009;10:31.
27. Beck S, Shamim EA, Richardson SP, Schubert M, Hallett M. Inter-hemispheric inhibition is impaired in mirror dystonia. *Eur J Neurosci* 2009;29:1634–1640.
28. Ni Z, Anastakis DJ, Gunraj C, Chen R. Reversal of cortical reorganization in human primary motor cortex following thumb reconstruction. *J Neurophysiol* 2010;103:65–73.
29. Chen R, Anastakis DJ, Haywood CT, Mikulis DJ, Manktelow RT. Plasticity of the human motor system following muscle reconstruction: a magnetic stimulation and functional magnetic resonance imaging study. *Clin Neurophysiol* 2003;114:2434–2446.
30. Cohen LG, Hallett M. Hand cramps: clinical features and electromyographic patterns in a focal dystonia. *Neurology* 1988;38:1005–1012.
31. Pal PK, Hanajima R, Gunraj CA, et al. Effect of low-frequency repetitive transcranial magnetic stimulation on interhemispheric inhibition. *J Neurophysiol* 2005;94:1668–1675.
32. Siebner HR, Filipovic SR, Rowe JB, et al. Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. *Brain* 2003;126:2710–2725.
33. Siebner HR, Tormos JM, Ceballos-Baumann AO, et al. Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. *Neurology* 1999;52:529–537.

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