

Ipsilateral corticospinal projections do not predict congenital mirror movements: A case report

T. Verstynen^{a,b,*}, R. Spencer^{a,b}, C.M. Stinear^c, T. Konkle^a,
J. Diedrichsen^d, W.D. Byblow^c, R.B. Ivry^{a,b}

^a Department of Psychology, University of California, Berkeley, CA, United States

^b Helen Wills Neuroscience Institute, University of California, Berkeley, CA, United States

^c Department of Sport and Exercise Science, University of Auckland, Auckland, New Zealand

^d Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States

Received 15 March 2006; received in revised form 11 August 2006; accepted 18 August 2006

Available online 4 October 2006

Abstract

Congenital mirror movements (CMMs) are involuntary, symmetric movements of one hand during the production of voluntary movements with the other. CMMs have been attributed to a range of physiological mechanisms, including excessive ipsilateral projections from each motor cortex to distal extremities. We examined this hypothesis with an individual showing pronounced CMMs. Mirror movements were characterized for a set of hand muscles during a simple contraction task. Transcranial magnetic stimulation (TMS) was then used to map the relative input to each muscle from both motor cortices. Contrary to our expectations, CMMs were most prominent for muscles with the strongest contralateral representation rather than in muscles that were activated by stimulation of either hemisphere. These findings support a bilateral control hypothesis whereby CMMs result from the recruitment of both motor cortices during intended unimanual movements. Consistent with this hypothesis, bilateral motor cortex activity was evident during intended unimanual movements in an fMRI study. To assess the level at which bilateral recruitment occurs, motor cortex excitability during imagined unimanual movements was assessed with TMS. Facilitory excitation was only observed in the contralateral motor cortex. Thus, the bilateral recruitment of the hemispheres for unilateral actions in individuals with CMMs appears to occur during movement execution rather than motor planning.

© 2006 Elsevier Ltd. All rights reserved.

Keywords: Mirror movements; Corticospinal; fMRI; EMG; TMS; Motor control; Motor cortex

The ability to move one hand while keeping the other at rest is a ubiquitous characteristic of human motor control. Under certain conditions, however, the independent control of the hands is diminished; when attempting to move one hand, involuntary activation of homologous muscles in the other hand is observed, a phenomenon referred to as mirror movements. Mirror movements are common during normal human development and usually disappear after the complete myelination of the corpus callosum (Mayston, Harrison, & Stephens, 1999; Muller, Kass-Iliyya, & Reitz, 1997; Wolff, Gunnoe, & Cohen 1985). Adults may also exhibit mirror movements when executing difficult uni-

manual actions (Aranyi & Rosler, 2002) or following damage to cortical and subcortical areas of the brain (Farmer, 2005; Nelles, Cramer, Schaechter, Kaplan, & Finklestein, 1998; Rocca et al., 2005).

Some individuals manifest mirror movements throughout their lifetime (Schott & Wyke, 1981). This condition may be associated with developmental abnormalities such as in Klippel–Fiel syndrome or X-linked Kallmann's syndrome, or may be present even in the absence of other neurological or peripheral abnormalities (for review see Vulliemoz, Raineteau, & Jabaudon, 2005). For the latter group, mirror movements are frequently observed in multiple family members, indicating a genetic basis. These behaviors are referred to as congenital mirror movements (CMMs).

CMMs have been associated with abnormal descending corticospinal projections. Studies using transcranial magnetic

* Corresponding author at: Cognition and Action Laboratory, Department of Psychology, 3210 Tolman Hall, University of California, Berkeley, CA 94720, United States. Tel.: +1 510 642 0135; fax: +1 510 642 5293.

E-mail address: timothyv@gmail.com (T. Verstynen).

stimulation (TMS) have found that, in persons afflicted with CMMs, stimulation over either hemisphere can evoke muscle activity bilaterally (Balbi, Trojano, Ragno, Perretti, & Santoro, 2000; Britton, Meyer, & Benecke, 1991; Farmer, Ingram, & Stephens, 1990; Konagaya, Mano, & Konagaya, 1990). Moreover, the latencies of motor evoked potentials (MEPs) in the ipsi- and contralateral hand were identical (Cohen et al., 1991), arguing against the idea that the ipsilateral responses are mediated transcallosally. The observation of bilateral evoked responses has led to the general consensus that CMMs reflect unilateral control signals that are projected bilaterally. According to this unilateral control hypothesis, commands from the motor cortex used to produce volitional movements with the contralateral hand are, at least weakly, also projected by ipsilaterally descending projections to homologous muscles, thus resulting in mirror movements. Recently, however, this hypothesis has come under increasing doubt given the observations that persons with CMMs exhibit bilateral activity of the motor cortex during intended unimanual movements (Krams et al., 1997; Leinsinger et al., 1997; Mayer, Schulze, Danek, & Botzel, 1999) and that the ipsilateral projections from the motor cortex are independent from the descending contralateral projections (Balbi et al., 2000; Cincotta et al., 2003).

The expression of CMMs is primarily, if not exclusively, limited to the distal muscles of the hands and wrists (Schott & Wyke, 1981). Previous studies have focused on characterizing the organization of corticospinal projections to one or two intrinsic hand muscles (Balbi et al., 2000; Britton et al., 1991; Cohen et al., 1991; Cincotta et al., 1994, 2003; Konagaya et al., 1990). However, little is known regarding whether and how CMMs vary across a range of distal muscles. This information could help elucidate the underlying physiological mechanisms of the disorder. For example, if CMMs are caused by an abnormal quantity of uncrossed corticospinal projections, as suggested by the unilateral control hypothesis, then across a set of muscles, one would expect to observe a correlation between the magnitude of CMMs expressed behaviorally and ipsilateral MEPs elicited by TMS.

We report here an extensive case study of an individual with CMMs. We examined the distribution of mirror movements across a set of hand muscles and assessed the relative input from each cortical hemisphere using TMS. There was considerable heterogeneity in both the degree of CMMs and the muscle innervation patterns. Indeed, some muscles were exclusively activated by contralateral TMS, others exclusively by ipsilateral TMS, with only a few showing pronounced bilateral influence. Moreover, contrary to the prediction of the unilateral control hypothesis, we failed to observe a relationship between the degree of CMMs and the muscle innervation patterns. The level of emergence of CMMs was additionally examined with fMRI and a motor imagery task. These findings further support the emerging hypothesis that CMMs arise from bilateral engagement of the motor cortices rather than bilateral projections from a single motor cortex. We suggest that, at least for the individual studied here, this bilateral recruitment is likely due to the distributed representation of hand muscles across the two hemispheres.

1. Methods

1.1. Participants

OL is a 25-year old male with CMM. He is strongly right handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). During informal observation, mirror movements can easily be seen when OL moves his hands or wrists, with no obvious asymmetry between the two hands. There are no detectable CMMs in the arm proximal to the wrist or in the lower limbs. OL reports that his father also exhibits similar CMMs. Other than the involuntary mirror movements, OL has no history of neurological abnormalities. His developmental history is normal and OL finds that the CMMs have minimal effect on his everyday skills.

Three neurologically healthy right-handed participants (ages 25, 31, 32, all males) were recruited as controls for the behavioral tasks and TMS mapping study. For the functional imaging study, OL's performance was compared to a group of eight right handed participants (four male, four female) whose results have been reported in a previous study (Verstynen, Diedrichsen, Albert, Aparicio, & Ivry, 2005). All participants provided informed consent under a protocol approved by the IRB at UC Berkeley.

1.2. Assessment of mirror movements

For OL and the control participants, electromyographic (EMG) activity was recorded from twelve muscles (Fig. 1a). For each hand, EMG was recorded from two intrinsic hand muscles (first dorsal interosseous, FDI; abductor pollicis brevis, APB), three extrinsic hand muscles (extensor indicis proprius, EIP; extensor digitorum communis, EDC; flexor digitorum superficialis, FDS) and one wrist muscle (extensor carpi radialis, ECR). All EMG activity was recorded using bipolar surface electrodes sampling at a rate of 2 kHz without band-pass filtering of the signal (Delsys Inc.).

To measure the expression of CMMs on a muscle-by-muscle basis, the participant was instructed to maximally contract the target muscle with one hand while relaxing the other hand. The contraction was performed freely in the air and not against a surface. A tone was presented to initiate each trial. The participant was instructed to wait approximately 1 s and then contract the target muscle. Six target actions were selected:

- FDI: Abduction of the second digit.
- APB: Flexion of the metacarpalphalangeal joint of the thumb.
- EIP: Extension of the second digit while maintaining the other digits at rest.
- FDS: Flexion of the proximal interphalangeal joint of the second through fifth digits.
- EDC: Extension of the metacarpalphalangeal of the second through fifth digits.
- ECR: Extension and radial deviation of the wrist.

Maximum contraction of the targeted muscle was maintained for approximately 4 s. Participants were then instructed to relax for approximately 30 s before the next trial. Each of the target actions was repeated for 10 consecutive trials. For OL, recordings from intrinsic and extrinsic muscles were performed on different days due to a limited number of EMG channels, but the full set of 12 actions (6 actions \times 2 hands) were tested on both sessions. For the control participants, only a subset of eight muscles was tested in a single session (left and right ECR, EIP, FDI and APB). We did not test these participants in a second session given the dramatic difference between their results and those obtained with OL (see below). The control data set also does not include contractions of the EIP muscles in one subject, due to erroneous electrode placements.

When participants produced the target action with the volitional hand, we sometimes observed contractions in both homologous and non-homologous muscles of the other hand. It is important to note that, during the volitional actions, activation in the target hand was not restricted to the target muscle. Thus, it is difficult to determine whether the non-volitional activity in the other hand was specific to homologous muscle pairs or resulted from cross-talk with non-homologous muscles. Thus, for our analysis on the expression of mirror movements, we focused only on homologous muscle pairs.

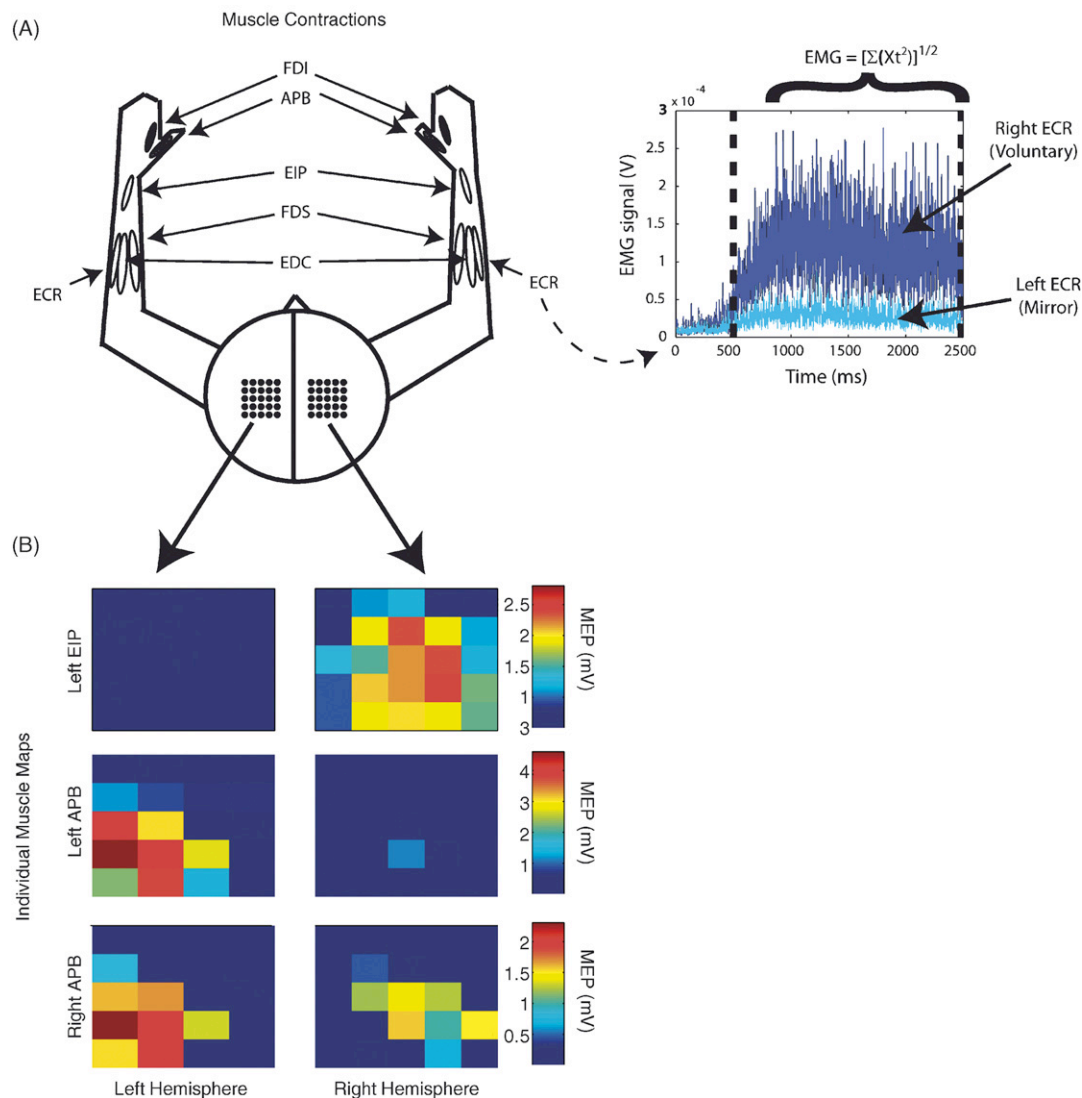


Fig. 1. (A) Six muscles in each hand were monitored for involuntary mirror movements during voluntary contraction of the contralateral hand. (B) Transcranial magnetic stimulation (TMS) was applied over a grid of points over the motor cortex of each hemisphere. Each muscle's response to TMS was remapped onto the grid using a reverse-correlation procedure (see text) to generate a scalp map of the representation of each muscle (lower left panels). The color scale is used to indicate the induced motor-evoked potential (MEP) amplitude for each stimulation site. Three representative muscles are depicted in this figure.

1.3. EMG analysis

EMG was sampled at 2 kHz. The signal from each muscle was rectified and the EMG onset of voluntary contraction was visually determined for every trial based on a graphical display of the rectified signal. For each member of a pair of homologous muscles, the intensity of the EMG signal was quantified by taking the root mean square (RMS) value of the signal for the first 2 s following movement onset. A mirror score for each muscle was calculated by comparing its activation level when the target posture was adopted by the other hand (mirror-based activity) compared to when the target posture was adopted by that muscle (voluntary activity). This score was quantified as:

$$\text{mirror movement} = \sum \left[\frac{\text{RMS}(mX_t)}{\text{median}(\text{RMS}(vX))} \right] \times \frac{1}{N};$$

The value mX_t represents the vector of EMG values on a given trial (t) in a muscle when it is mirroring the contralateral hand. Each value is normalized by the activity of this same muscle when it was voluntarily contracted, using the median RMS (vX) over the 10 voluntary-contraction trials. These values are averaged across all trials (N) to give an average mirror score for that muscle.

Thus, the mirror score represents the magnitude of a CMM in a muscle as a proportion its activity during voluntary contraction. Muscles that do not express involuntary activity have a mirror score at or near 0. Muscles with equivalent levels of involuntary and voluntary activity have a mirror score near 1. Similar measures have been used in previous studies of CMMs (Hermsdorfer, Danek, Winter, Marquardt, & Mai, 1995).

1.4. Motor cortex mapping

TMS was used to map the motor cortical representations of individual muscles (Wilson, Thickbroom, & Mastaglia, 1993). We mapped each of the muscles tested in the contraction task described above. Stimulation was performed with a 70 mm figure-eight coil driven by a Magstim standard rapid stimulator (Magstim Inc.). For OL, two mapping sessions were performed on separate days: one for intrinsic hand muscles and one for extrinsic muscles. For the control participants, only one mapping session was performed. For each session the participant was fitted with a snug plastic shower cap and a small grid of 1 cm spaced points was drawn on the inter-aural line, centered 3–4 cm lateral to the vertex (4 cm \times 5 cm for intrinsic muscles in OL; 5 cm \times 5 cm for extrinsic

muscles in OL and all muscles in control participants). In normal participants, the optimal coil-orientation required for eliciting responses in ipsilateral hand muscles differs from the best orientation required for eliciting responses in contralateral muscles (Ziemann et al., 1999). In order to avoid a bias for one response type over another, the coil was oriented along the anterior-posterior direction, half-way between the optimal orientations for eliciting contralateral and ipsilateral responses. Stimulator output was set at an intensity that (a) elicited at least 30 μ V MEPs in all the muscles at 1 or more grid positions and (b) produced no response at 2 or more grid positions. The latter criterion was adopted to increase specificity by preventing saturation of the map area for a particular muscle.

For the mapping procedure, participants were instructed to relax all of their hand muscles during stimulation. Six consecutive stimuli were delivered over each grid position, with the order of the positions selected at random. The stimuli were separated by a minimum of 5 s. The peak-to-peak amplitude of the MEPs (unrectified signal) was calculated for each muscle on each trial.

The map volume (V) for each muscle representation was calculated as

$$V = \sum (P_{xy})$$

Map volume is the sum of the median MEP values across all points on the grid (P_{xy}). The map volume asymmetry for each muscle was then calculated to give a muscle representation (MR) score.

$$\text{muscle representation} = \frac{(\text{Vipsi})}{(\text{Vipsi} + \text{Vcontra})}$$

A muscle representation score of 1 indicates that the muscle is only represented in the ipsilateral hemisphere and a score of 0 indicates that the muscle is only represented in contralateral motor cortex. A score of 0.5 indicates that the muscle is represented in the left and right hemispheres equally. If the estimated MEP amplitude for a given location did not exceed 1.5 times the background EMG level, the value for that location was set to 0. This criterion minimized the artificial inflation of the degree of bilateral representation, since scores greater than zero required that a minimal EMG response was elicited for a given observation.

The latency of MEPs was estimated by visually determining the onset of each MEP. For each muscle, the optimal grid position for eliciting MEPs was determined from the scalp maps described above. In cases of muscles with Muscle Representation scores near 0.5, one point from each hemisphere was identified. Trials in which TMS was applied over these optimal points were used to assess the latency of contralateral and ipsilateral MEPs.

1.5. fMRI procedures

OL was tested in a single fMRI session to assess hemodynamic responses in the motor cortex during various types of tasks involving unilateral finger movements. Scanning was performed with a Varian 4T Unity INOVA system. High resolution gradient-echo (GEM) images were acquired along the axial plane as localizer images (18 slices, matrix size = 256 \times 256, thickness = 3 mm, gap = 0.5 mm). The field-of-view (22.4 cm \times 22.4 cm \times 6.3 cm) for these images encompassed all cortical regions above the Sylvian fissure. A total of 1300 functional volumes were acquired across four consecutive scans using an echoplanar imaging pulse sequence (EPI parameters: 18 slices interleaved, TR = 2000 ms, TE = 28 ms, matrix size = 64 \times 64, thickness = 3 mm, gap = 0.5 mm, yielding isotropic voxels of 3.5 mm size) sensitive to blood oxygenated level dependent (BOLD) changes. The onset of each functional scan was synchronized to the onset of each task-relevant event, including the instruction and imperative stimuli, as well as the onset of the delay and rest periods. These events were modeled as box-car functions and convolved with the participant's hemodynamic response function assessed during a control task (see Verstynen et al., 2005). The angle and orientation of the functional slices were identical to those of the GEM images used for structural localization. A high resolution T1-weighted image was acquired using a FLASH pulse sequence (91 slices, matrix size = 91 \times 109, thickness = 2 mm). This image was used for spatial normalization using SPM2.

The task was identical to that described in a previous study (Verstynen et al., 2005). Briefly, participants were situated comfortably in the scanner with a

vacuum-adjusted foam pad to reduce head movement. All responses were made on two five-key piano-style keyboards, one under each hand. Stimuli were displayed on a front-projecting display system. Each trial began with an instruction period in which cues were provided to signal the required hand, movement type, and specific fingers for the forthcoming trial. Five horizontal lines were displayed on the screen to represent the five fingers of the target hand. These lines were shifted approximately 3° to the left of center to indicate a left-hand trial and 3° to the right of center to indicate a right-hand trial.

There were three types of movements. The sequence task involved the cyclical production of a four-finger sequence. The numbers one to four appeared over four of the five lines, indicating the order in which the keys had to be pressed. For the chord task, the participant was required to press and release a set of three keys simultaneously. The three fingers required for the chord were indicated by Xs appearing above three of the lines. The chord response alternated with a single response produced by the thumb in order to ensure that the fingers were reconfigured prior to each chord response. Finally, the simple tap task involved repetitive tapping with a single finger. On these trials, a single "X" appeared over one of the four lines, indicating the finger to be used.

The instruction screen remained visible for 2 s. Following this, the screen was blank for 2–6 s. During this period, participants were instructed to prepare the response while avoiding overt movements. Immediately following this preparation period, a green "Go" was displayed on the screen and participants were instructed to produce the target movement as many times as possible within a 4 s movement period. The word "Stop" indicated the end of the trial.

Data were analyzed using an anatomical region of interest (ROI) method that involves generating voxel maps over the left hemisphere and right hemisphere precentral gyrus using the non-normalized GEM image as a template. The ROI was restricted to voxels on the precentral gyrus and the anterior portions of the central sulcus to minimize the influence of somatosensory activation (Verstynen et al., 2005). Task-related voxels (with $t > 2.75$) were identified in each precentral ROI using a modified general linear model (GLM; Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). The number of task related voxels in the ipsilateral precentral gyrus, as a proportion of the total number of significant voxels in both gyri, was used as our dependent variable. This measure was used in Verstynen et al. (2005), allowing us to compare OL with a group of right-handed control participants.

1.6. Motor Imagery Task

TMS was used to evaluate changes in corticomotor excitability while OL performed a simple kinesthetic motor imagery task involving the thumb of the right hand (see Stinear, Byblow, Steyvers, Levin, & Swinnen, 2006). The right APB was chosen because it was found to have a strong bilateral representation in the TMS mapping experiment. The optimal locations for inducing MEPs with the coil angled approximately 45° from the frontal plane in the ipsilateral (right) and contralateral (left) hemispheres were identified and marked on the cap. In order to maximize the sensitivity of our ability to detect excitability changes in MEP amplitude, the intensity of magnetic stimulation was set to produce a MEP of half of the maximum amplitude possible at rest. This level was determined for each hemisphere and used for the remainder of the experiment to ensure maximum sensitivity to changes in corticospinal excitability (Devanne, Lavoie, & Capaday, 1997).

Twelve MEPs were collected while OL rested both hands on the table surface. Following these rest trials, stimuli were delivered during 48 imagery trials. OL's task was to imagine the "kinesthetic sense of using your thumb to press and hold the space key on a keyboard." Before the start of each trial, OL was instructed as to which thumb to imagine using. A short tone (50 Hz, 500 ms) cued OL to commence imagining the target action, while keeping his hands at rest. Approximately 2 s after the tone, a single TMS pulse was delivered over either the left or right hemisphere. The trial was terminated after 4 s. There were four imagery task conditions (2 hemisphere \times 2 imagery hand) and 12 right APB MEPs were recorded under each of these conditions, in a random trial order.

MEP amplitude and background EMG (the RMS calculated over a 50 ms window prior to the TMS pulse) were determined during the four imagery conditions. To minimize the influence of involuntary contractions of the target muscle on the MEP measures, we excluded trials in which the background EMG exceeded 15 μ V. Based on this criteria, 17% of the trials were excluded.

2. Results

2.1. Mirror movements and cortical projections

As expected, there was little, if any, expression of mirror activity for the 22 muscles tested across the three control participants (mirror movement scores ranged from 0.009 to 0.292; 0.06 ± 0.07 mean and standard deviation). In contrast, OL exhibited substantial mirror movements, although the expression of these varied across the 12 muscles. Mirror movements were most prominent during contractions of extrinsic hand and wrist muscles. In fact, for the left EIP and right FDS, the mirror-related EMG activity during contraction of the homologous muscle for the other hand was as large as during voluntary contraction of these muscles. This pattern was markedly reduced for the intrinsic hand muscles APB and FDI. From the control data, we calculated 95% confidence intervals based on all 22 muscles tested. OL's mirror movement scores were outside this interval in 8 of the 12 muscles. Mirror movement scores were within the normal bounds only for the right hand EDC and FDI and left hand FDS and APB.

Using TMS, we tested the degree of contralateral and ipsilateral input to the eight target muscles in each of the control participants. Of the 24 possible muscles, we were only able to obtain MEPs in 19 muscles; the other five were not activated following stimulation over any cortical site tested (left ECR in participant 1; right EIP and left EIP, FDI, APB for participant 2). MEPs were only observed in the hand contralateral to the stimulation. For all of the control muscles tested, the activation was much stronger following contralateral stimulation, reflected in muscle representation scores that ranged from 0.00 to 0.17 (mean = 0.02 ± 0.04). Based on these data, the upper bound for a 95% confidence interval is 0.10.

For OL, MEPs were observed in all of the tested muscles. The muscle representation score fell within the control-defined confidence interval for only two muscles, left and right EIP. Nonetheless, there was considerable variability of these scores (Fig. 1b). Many muscles, especially the extrinsic hand and wrist muscles, were mainly activated with contralateral stimulation. In contrast, the intrinsic hand muscles had more diverse representation patterns. MEPs were almost exclusively elicited following ipsilateral stimulation in some muscles, such as the left APB and both FDI. MEPs in the right APB muscle, in comparison, were observed with approximate equal frequency and amplitude following stimulation of either the left or right motor cortices, suggesting a bilateral representation. This bilateral pattern was also observed in the left flexor complex (FDS). Interestingly, for the two muscles showing bilateral responses, the latencies at which the MEPs reached their peak amplitudes were delayed by 5 ms relative to the ipsilateral MEP latencies (Fig. 2). The longer latency of contralateral MEPs in OL suggest at least one additional synapse may occur within the cortex, sub-cortically, or both.

Contrary to the unilateral control hypothesis, CMMs were generally strongest in muscles for which MEPs were elicited by contralateral stimulation. The correlation between muscles exhibiting the largest CMMs and those in which MEPs are asso-

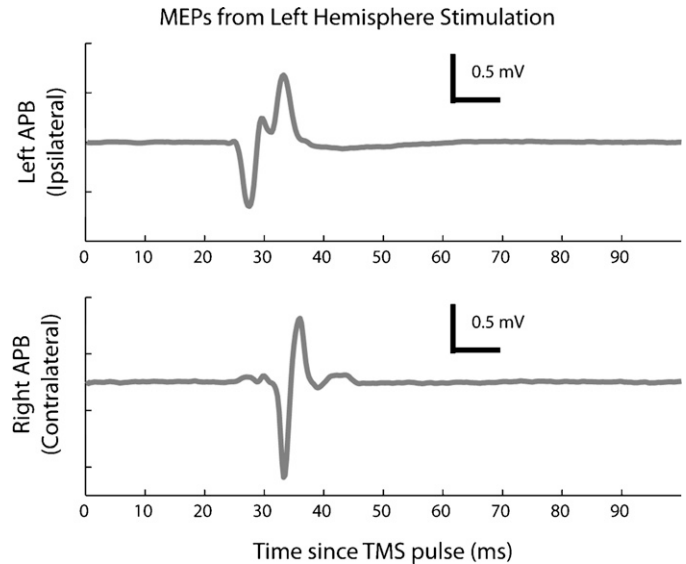


Fig. 2. Examples of ipsilaterally and contralaterally produced MEPs in one muscle pair (APB). The contralateral MEP begins about 5 ms after the onset of the ipsilateral MEP.

ciated with ipsilateral TMS was negative (Fig. 3; Spearman's $r = -0.60$, $p = 0.04$). Fig. 4 shows schematic representations of the projections to each muscle from the left and right motor cortex. From this perspective we see two occurrences of strong bilateral projections (APB and FDS) from the left hemisphere and two instances of weak bilateral projections (ECR and EDC) from the right hemisphere. In every instance of bilateral projections, however, the ipsilateral muscle shows a very weak degree of CMMs (see Fig. 3). Thus by looking at the corticospinal projections from either a muscle-centric or cortical-centric perspective, it is clear that the ipsilateral fibers do not play a significant role in the expression of CMMs.

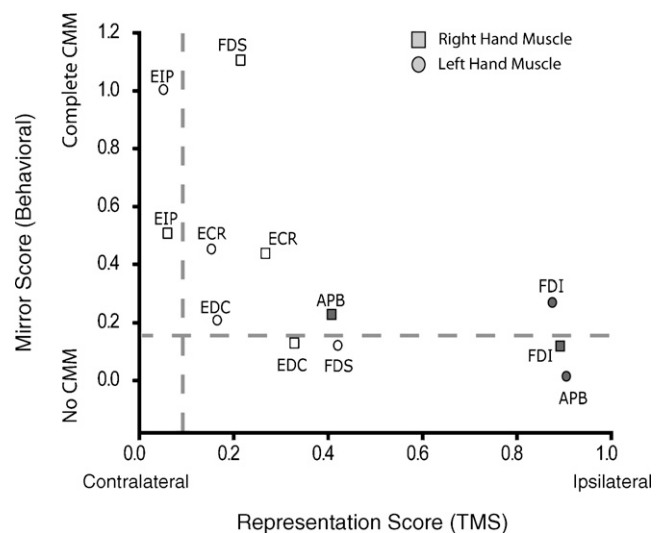


Fig. 3. Relationship between degree of involuntary mirror movements and cortical innervation asymmetries. Intrinsic hand muscles are shown as filled points while extrinsic hand and wrist muscles are indicated by the open points. The dashed lines represent the upper bounds of the 95% confidence intervals estimated from control participants.

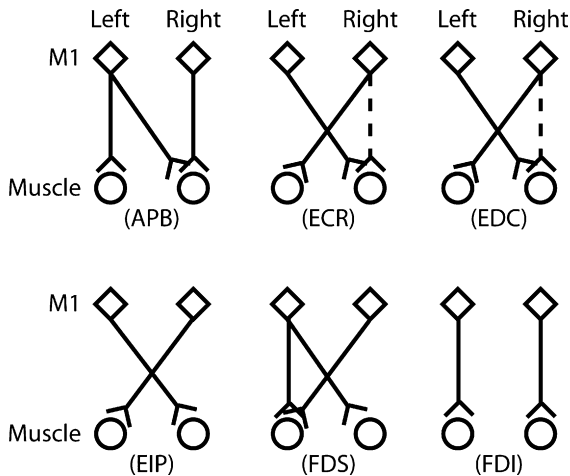


Fig. 4. Schematic representation of the corticospinal projections for each muscle pair in OL. Dashed lines indicate weaker pathways.

2.2. Precentral gyrus activation during movement

fMRI was performed while OL attempted to produce three types of unimanual movements: simple finger tapping, complex configural chord like movements, and sequential finger movements.

In all three conditions, the activation pattern was bilateral. For example, during left hand tapping, 33% of the significantly activated voxels were in the ipsilateral precentral gyrus. This value is 1.8 standard deviations away from a mean value based on data obtained in a previous imaging study involving neurologically healthy right handed participants (Verstynen et al., 2005). For right hand tapping, this percentage increased to 37% (0.69 standard deviations above the control mean). The bilateral recruitment of precentral gyrus was even more extensive during the more complex movements (Fig. 5). When producing left hand sequences and chords, the percentage of significantly activated voxels in the left, ipsilateral hemisphere was 42% and 40%, respectively (0.56 and 0.5 standard deviations away from control means). During right hand movements, the percentages increased to 53% and 56% for the sequence and chord tasks (both values are 1.8 standard deviations greater than control means).

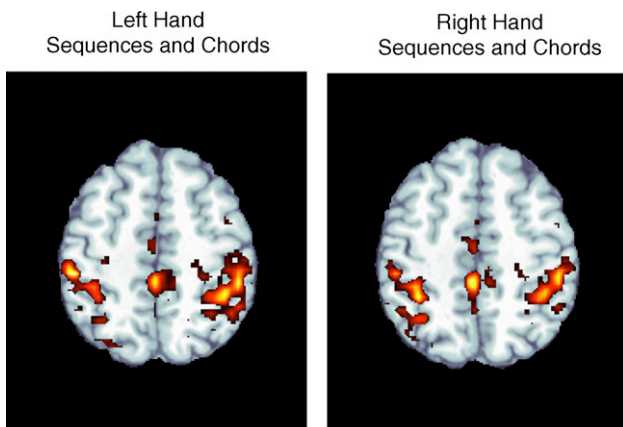


Fig. 5. Regions of significant activation, assessed by fMRI, during voluntary left and right hand multi-finger movements for OL compared to rest.

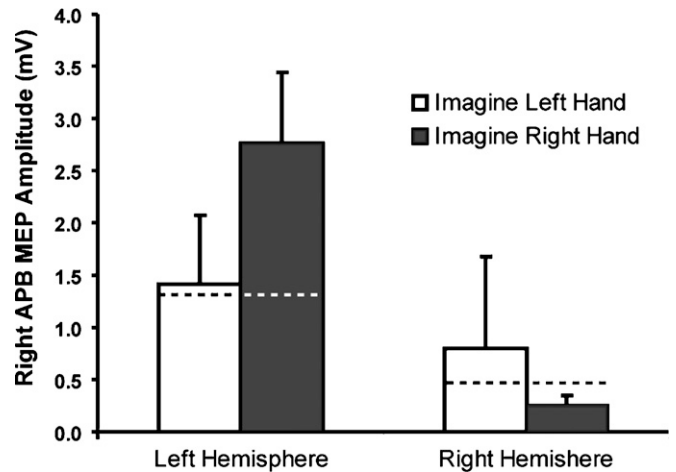


Fig. 6. MEPs in the right APB as a result of motor imagery. Dashed lines represent baseline MEP amplitudes during rest. Error bars reflect one standard deviation.

Thus, OL actually shows slightly greater activation in the right hemisphere during right hand movements.

Similar to reports in other individuals with CMMs (Krams et al., 1997; Leinsinger et al., 1997; Maegaki et al., 2002; Mayer et al., 1999), OL exhibits a response in both motor cortices when attempting to move just one hand.

2.3. Motor imagery and the premotor signal

Average MEP amplitudes at rest were 1.4 and 0.5 mV for left and right hemisphere stimulation, respectively. Right APB MEPs in response to left hemisphere stimulation increased by 97% during right hand imagery, but remained at baseline levels during left hand imagery. With right hemisphere stimulation, the right APB MEPs increased by 58% during left hand imagery, and decreased 51% during right hand imagery (Fig. 6). Thus, when OL imagines executing a unimanual movement the contralateral corticomotor pathways are facilitated (meaning, he does not have mirror “imagined” movements). This suggests that the premotor input to M1 is normally lateralized for OL and the mirror movements arise from an interaction of the two motor cortices during the execution of the movement.

3. Discussion

Various physiological mechanisms have been proposed concerning the etiology of CMMs. Prominent among these is the unilateral control hypothesis, which states that mirror movements arise when a volitional motor command is sent from one motor cortex to homologous muscles in the contralateral and ipsilateral hand due to an excessive degree of uncrossed descending corticospinal projections (Britton et al., 1991; Cohen et al., 1991; Cincotta et al., 1994; Farmer et al., 2004; Konagaya et al., 1990). Recent studies, however, argue against this hypothesis. For example, functional imaging studies show a strong bilateral engagement of the motor cortices during intended unimanual movements in persons afflicted with CMMs (Krams et al., 1997; Leinsinger et al., 1997; Maegaki et al., 2002; Mayer et al., 1999).

In addition, ipsilateral and contralateral TMS-induced responses do not always show identical profiles in persons with CMMs, suggesting that they may arise from independent descending pathways (Balbi et al., 2000; Cincotta et al., 2003) rather than bifurcating projections from the same corticospinal pathway (Farmer et al., 1990). This has led to the emergence of a bilateral control hypothesis, whereby CMMs are mediated by a mutual engagement of the two motor cortices during intended unimanual movements.

Our results do not conform to the unimanual control hypothesis in many ways. First, rather than a consistent picture of bilateral corticospinal projections, the projection pattern in OL was quite varied. Some muscles were only activated by contralateral TMS, others predominantly by ipsilateral TMS (see also, Pohja, Salenius, & Hari, 2000; Ueki et al., 2005) and a few by TMS over either motor cortex. In cases where a muscle received input from both motor cortices, ipsilaterally induced MEPs occurred about 5 ms before MEPs in the contralateral muscles. This is in contrast to previous findings showing that MEPs in ipsilateral and contralateral muscles occur at approximately the same time (Cohen et al., 1991). An explanation of this discrepancy requires further investigation. The asymmetry in MEP latencies in OL may reflect a unique feature of his corticospinal projections; alternatively, this may represent another form of heterogeneity in muscle innervation patterns which may be present in individuals with CMMs.

Second, the relationship between mirror movements and the cortical representation of individual muscles is at odds with the unimanual control hypothesis. This hypothesis predicts that the degree of CMMs should be directly related to the degree of bilateral cortical representation. In OL's case, the muscles which exhibited the strongest mirror movements were those that are driven mainly by the contralateral motor cortex. Thus, our direct comparison of cortical input lateralization and mirror movements did not support the prediction that abnormal ipsilateral projections mediate CMMs.

Finally, using fMRI, we observed strong bilateral activation of the primary motor cortex during both simple and more complex unimanual movements. A strong version of the unimanual control hypothesis is that activation during unimanual movements should be restricted to the contralateral hemisphere. In contrast, there was considerable bilateral motor cortex activation during the execution of unimanual movements (see also Krams et al., 1997; Leinsinger et al., 1997; Maegaki et al., 2002; Mayer et al., 1999).

There are, however, two important caveats to keep in mind when considering the fMRI data. First, bilateral activation during unimanual movements is observed in individuals who do not express CMMs (Cramer, Finklestein, Schaechter, Bush, & Rosen, 1999; Kawashima et al., 1993; Kim et al., 1993; Singh et al., 1998; Kobayashi et al., 2003; Verstynen et al., 2005). OL's activation pattern is, in a sense, an exaggeration of the pattern found in normal individuals, with his bilateral engagement manifest for both simple and complex movements. Second, when OL is attempting to execute unimanual movements, the other hand is moving; i.e., he expresses CMMs. The enhanced bilateral activation pattern may be a consequence of the CMMs rather than

a direct reflection of control activity required to produce the volitional movements (see also Krams et al., 1997). The mirror movements surely generate sensory signals and these may help drive the cortical activation pattern or the bilateral activity may reflect the recruitment of mechanisms that can be used to inhibit or attenuate the unwanted mirror movements. As such, the current imaging data, while consistent with the bilateral control hypothesis, must be interpreted cautiously.

The findings from the motor imagery study suggest that the engagement of both motor cortices during unimanual movements is specific to processes associated with movement execution. Imagined actions increased excitability in the motor cortex contralateral to the imagined hand. In addition, motor imagery of the right hand was associated with a decrease in right motor cortex excitability. Similar decreases in excitability have been observed in healthy adults during ipsilateral hand movements and are thought to be due to callosally mediated inhibition from the contralateral cortex (Liepert, Dettmers, Terborg, & Weiller, 2001). Thus, when imagining a movement, facilitation is restricted to a single hemisphere, in a manner similar to that observed in individuals without CMMs (Stinear et al., 2006). We hypothesize that planning processes are lateralized in OL; for example, imagining a right hand movement primarily engages planning-related activity in motor and premotor regions in the left hemisphere. The increase in excitability thus reflects a priming effect from this planning process, even though the actual recruitment of muscle-specific cortical units does not occur, at least not to a measurable level. The functionality of this modulation is not clear. Nonetheless, the strictly lateralized effect suggests that the mechanisms mediating mirror movements are only engaged during the execution of hand actions.

We propose that rather than arising from ipsilateral collaterals of descending corticospinal fibers, the CMMs may result from an adaptive strategy OL must use to control his hand movements due to the abnormal organization of his corticospinal pathways. Specifically, given the heterogeneity of his cortical projections to each hand, he must recruit both motor cortices when executing a unimanual action. Consider the relatively simple act of grasping a pencil with the left hand (Fig. 7). OL must recruit muscles that are primarily activated by the right motor cortex (EIP and EDC), a muscle that is equally activated by both hemispheres (FDS), and another pair of muscles that are activated by the left motor cortex (FDI and APB). Thus both motor cortices are extensively engaged during this unimanual movement. The presence of mirror movements suggests that OL is unable to meet these idiosyncratic recruitment requirements with precise control. Signals associated with the recruitment of particular muscles appear to be broadcast to both hemispheres, even for muscles that are controlled by a single hemisphere. In this sense, his mirror movements are an emergent property of the bilateral recruitment of the motor cortices due to the heterogeneous pattern of muscle representation hemispheres.

It is puzzling that in OL mirror movements are especially prominent in contralaterally innervated muscles. While this is at odds with the unilateral control hypothesis, a simple application of the bilateral control hypothesis would suggest either an equivalent level of CMMs for all muscles or that muscles with

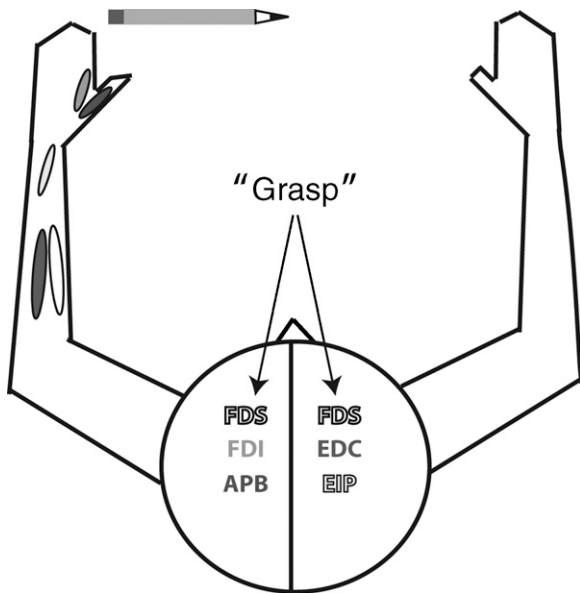


Fig. 7. If OL is to execute a simple action like grasping a pencil with his left hand, his brain must coordinate a heterogeneous set of muscles. One way this may happen is to execute the same command with both hemispheres.

strongly lateralized inputs, either contra- or ipsilateral, would be the least susceptible to mirror movements. At present, we can only speculate on this issue. One possibility is that transcallosal mechanisms may modulate the degree of CMMs, similar to how such mechanisms influence bilateral motor cortex activity in normal participants (Kobayashi, Hutchinson, Schlaug, & Pascual-Leone, 2003). For example, uncrossed projections to distal muscles may experience more interhemispheric inhibition compared to contralaterally projecting neurons or be at the mercy of different excitatory inputs. Elucidating these mechanisms is a challenge for future investigation.

References

- Aranyi, Z., & Rosler, K. M. (2002). Effort-induced mirror movements. A study of transcallosal inhibition in humans. *Experimental Brain Research*, *145*, 76–82.
- Balbi, P., Trojano, L., Ragno, M., Perretti, A., & Santoro, L. (2000). Patterns of motor reorganization in a patient with mirror movements. *Clinical Neurophysiology*, *111*, 318–325.
- Britton, T. C., Meyer, B. U., & Benecke, R. (1991). Central motor pathways in patients with mirror movements. *Journal of Neurology, Neurosurgery, and Psychiatry*, *54*, 505–510.
- Cincotta, M., Ragazzoni, A., de Scisciolo, G., Pinto, F., Maurri, S., & Baroncini, F. (1994). Abnormal projection of corticospinal tracts in a patient with congenital mirror movements. *Neurophysiologie Clinique*, *24*, 427–434.
- Cincotta, M., Borgheresi, A., Balzini, L., Vannucchi, L., Zeloni, G., Ragazzoni, A., et al. (2003). Separate ipsilateral and contralateral corticospinal projections in congenital mirror movements: Neurophysiological evidence and significance for motor rehabilitation. *Movement Disorder*, *18*, 1294–1300.
- Cohen, L. G., Meer, J., Tarkka, I., Bierner, S., Leiderman, D. B., Dubinsky, R. M., et al. (1991). Congenital mirror movements. Abnormal organization of motor pathways in two patients. *Brain*, *114*, 381–403.
- Cramer, S. C., Finklestein, S. P., Schaechter, J. D., Bush, G., & Rosen, B. R. (1999). Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements. *Journal of Neurophysiology*, *81*, 383–387.
- Devanne, H., Lavoie, B. A., & Capaday, C. (1997). Input-Output properties and gain changes in the human corticospinal pathway. *Experimental Brain Research*, *114*, 329–338.
- Farmer, S. F. (2005). Mirror movements in neurology. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*, 1330.
- Farmer, S. F., Ingram, D. A., & Stephens, J. A. (1990). Mirror movements studied in a patient with Klippel–Feil syndrome. *Journal of Physiology*, *428*, 467–484.
- Farmer, S. F., Harrison, L. M., Mayston, M. J., Parekh, A., James, L. M., & Stephens, J. A. (2004). Abnormal cortex–muscle interactions in subjects with X-linked Kallmann’s syndrome and mirror movements. *Brain*, *127*, 385–397.
- Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping*, *1*, 214–220.
- Hermisdorfer, J., Danek, A., Winter, T., Marquardt, C., & Mai, N. (1995). Persistent mirror movements: Force and timing of “mirroring” are task-dependent. *Experimental Brain Research*, *104*, 126–134.
- Kawashima, R., Yamada, K., Kinomura, S., Yamaguchi, T., Matsui, H., Yoshioaka, S., et al. (1993). Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movements. *Brain Research*, *623*, 33–40.
- Kim, S. G., Ashe, J., Hendrich, K., Ellermann, J. M., Merkle, H., Ugurbil, K., et al. (1993). Functional magnetic resonance imaging of motor cortex: Hemispheric asymmetry and handedness. *Science*, *261*, 615–617.
- Kobayashi, M., Hutchinson, S., Schlaug, G., & Pascual-Leone, A. (2003). Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. *NeuroImage*, *20*, 259–270.
- Konagaya, Y., Mano, Y., & Konagaya, M. (1990). Magnetic stimulation study in mirror movements. *Journal of Neurology*, *237*, 107–109.
- Krams, M., Quinton, R., Mayston, M. J., Harrison, L. M., Dolan, R. J., Bouloux, P. M. G., et al. (1997). Mirror movements in X-linked Kallmann’s syndrome: II. A PET study. *Brain*, *120*, 1217–1228.
- Leinsinger, G. L., Heiss, D. T., Jassoy, A. G., Pfluger, T., Hahn, K., & Danek, A. (1997). Persistent mirror movements: Functional MR imaging of the hand motor cortex. *Radiology*, *203*, 545–552.
- Liepert, J., Dettmers, C., Terborg, C., & Weiller, C. (2001). Inhibition of ipsilateral motor cortex during phasic generation of low force. *Clinical Neurophysiology*, *112*, 114–121.
- Maegaki, Y., Seki, A., Suzuki, I., Sugihara, S., Ogawa, T., Amisaki, T., et al. (2002). Congenital mirror movement: A study of functional MRI and transcranial magnetic stimulation. *Developmental Medicine and Child Neurology*, *44*, 838–843.
- Mayer, M., Schulze, S., Danek, A., & Botzel, K. (1999). Dipole source analysis in persistent mirror movements. *Brain Topography*, *12*, 49–60.
- Mayston, M. J., Harrison, L. M., & Stephens, J. A. (1999). A neurophysiological study of mirror movements in adults and children. *Annals of Neurology*, *45*, 583–594.
- Muller, K., Kass-Iliyya, F., & Reitz, M. (1997). Ontogeny of ipsilateral corticospinal projections: A developmental study with transcranial magnetic stimulation. *Annals of Neurology*, *42*, 705–711.
- Nass, R. (1985). Mirror movement asymmetries in congenital hemiparesis: The inhibition hypothesis revisited. *Neurology*, *35*, 1059–1062.
- Nelles, G., Cramer, S. C., Schaechter, J. D., Kaplan, J. D., & Finklestein, S. P. (1998). Quantitative assessment of mirror movements after stroke. *Stroke*, *29*, 1182–1187.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*, 97–113.
- Pohja, M., Salenius, S., & Hari, R. (2000). Cortico-muscular coupling in a human subject with mirror movements—a magnetoencephalographic study. *Neuroscience Letter*, *327*, 185–188.
- Rocca, M. A., Mezzapesa, D. M., Comola, M., Leocani, L., Falini, A., Gatti, R., et al. (2005). Persistence of congenital mirror movements after hemiplegic stroke. *AJNR American Journal of Neuroradiology*, *26*, 831–834.
- Schott, G. D., & Wyke, M. A. (1981). Congenital mirror movements. *Journal of Neurology, Neurosurgery, and Psychiatry*, *44*, 586–599.

- Singh, L. N., Higano, S., Takahashi, S., Kurihara, N., Furuta, S., Tamura, H., et al. (1998). Comparison of ipsilateral activation between right and left hands: A functional MR imaging study. *Neuroreport*, 9, 1861–1866.
- Stinear, C. M., Byblow, W. D., Steyvers, M., Levin, O., & Swinnen, S. P. (2006). Kinesthetic, but not visual, motor imagery modulates corticomotor excitability. *Experimental Brain Research*, 168, 157–164.
- Ueki, Y., Mima, T., Oga, T., Ikeda, A., Hitomi, T., Fukuyama, H., et al. (2005). Dominance of ipsilateral corticospinal pathway in congenital mirror movements. *Journal of Neurology, Neurosurgery, and Psychiatry*, 76, 276–279.
- Verstynen, T., Diedrichsen, J., Albert, N., Aparicio, P., & Ivry, R. B. (2005). Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. *Journal of Neurophysiology*, 93, 1209–1222.
- Vulliemoz, S., Raineteau, O., & Jabaudon, D. (2005). Reaching beyond the midline: Why are human brains cross wired? *Lancet Neurology*, 4, 87–99.
- Wilson, S. A., Thickbroom, G. W., & Mastaglia, F. L. (1993). Transcranial magnetic stimulation mapping of the motor cortex in normal subjects. The representation of two intrinsic hand muscles. *Journal of Neurological Science*, 118, 134–144.
- Wolff, P. H., Gunnoe, C., & Cohen, C. (1985). Neuromotor maturation and psychological performance: A developmental study. *Developmental Medicine and Child Neurology*, 27, 344–354.
- Ziemann, U., Ishii, K., Borgheresi, A., Yaseen, Z., Battaglia, F., Hallett, M., et al. (1999). Dissociation of the pathways mediating ipsilateral and contralateral motor-evoked potentials in human hand and arm muscles. *Journal of Physiology*, 518, 895–906.