

Ipsilateral Motor Cortex Activity During Unimanual Hand Movements Relates to Task Complexity

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Verstynen, Timothy, Jörn Diedrichsen, Neil Albert, Paul Aparicio, and Richard B. Ivry. Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. *J Neurophysiol* 93: 1209–1222, 2005. First published November 3, 2004; doi:10.1152/jn.00720.2004. Functional imaging studies have revealed recruitment of ipsilateral motor areas during the production of sequential unimanual finger movements. This phenomenon is more prominent in the left hemisphere during left-hand movements than in the right hemisphere during right-hand movements. Here we investigate whether this lateralization pattern is related specifically to the sequential structure of the unimanual action or generalizes to other complex movements. Using event-related fMRI, we measured activation changes in the motor cortex during three types of unimanual movements: repetitions of a sequence of movements with multiple fingers, repetitive “chords” composed of three simultaneous key presses, and simple repetitive tapping movements with a single finger. During sequence and chord movements, strong ipsilateral activation was observed and was especially pronounced in the left hemisphere during left-hand movements. This pattern was evident for both right-handed and, to a lesser degree, left-handed individuals. Ipsilateral activation was less pronounced in the tapping condition. The site of ipsilateral activation was shifted laterally, ventrally, and anteriorly with respect to that observed during contralateral movements and the time course of activation implied a role in the execution rather than planning of the movement. A control experiment revealed that strong ipsilateral activity in left motor cortex is specific to complex movements and does not depend on the number of required muscles. These findings indicate a prominent role of left hemisphere in the execution of complex movements independent of the sequential nature of the task.

INTRODUCTION

A fundamental organizational principle of the human motor system is the contralateral control of distal movements. Reflected in part by the nearly complete crossing of corticospinal fibers innervating the distal musculature (Brinkman and Kuypers 1973), right-hand movements are associated with neural activity in the left motor cortex and left-hand movements with neural activity in the right motor cortex.

Similar to other aspects of brain function, the two hemispheres may not contribute in a symmetric manner to motor control. Neurologists have long noted that left hemisphere lesions are more likely to be associated with apraxia and that the symptoms are manifest in movements produced by either the right or left hand (Liepmann 1907). Physiological studies have also provided a challenge to the idea that the control of distal movements is exclusively contralateral. Single-cell re-

cordings in the primary motor cortex of the monkey show that a subset of neurons fire during both contra- and ipsilateral hand movements (e.g., Donchin et al. 2002; Tanji et al. 1988). In some human subjects, transcranial magnetic stimulation (TMS) over the hand notch of the motor cortex not only elicits motor-evoked potentials (MEPs) in contralateral but also in ipsilateral muscles. Finally, the optimal site to elicit an ipsilateral MEP is located lateral and ventral to the site of maximal contralateral MEP (Ziemann et al. 1999). This shift in the representation of ipsilateral hand movements has also been confirmed using functional brain imaging techniques (Cramer et al. 1999).

An interesting characteristic of the engagement of ipsilateral motor areas is that it is particularly strong during left-hand movements (Cramer et al. 1999; Kawashima et al. 1993; Kim et al. 1993; Kobayashi et al. 2003; Li et al. 1996; Nirkko et al. 2001; Singh et al. 1998). Here we investigate whether the preferential involvement of motor areas in the left hemisphere varies as a function of the characteristics of the action. Functional imaging studies of ipsilateral activity have almost exclusively relied on a task in which the thumb has to be opposed to the other fingers in a sequential order (Kawashima et al. 1993; Kim et al. 1993; Kobayashi et al. 2003; Nirkko et al. 2001; Singh et al. 1998). It is possible that the left-hemisphere activity during left-hand movements results from its involvement in the sequencing demands of the task rather than indicating a specialization of this hemisphere in motor control per se. In language, the dominance of the left hemisphere has been attributed to its ability to process sequential information (Corballis 1991). Furthermore, learning of motor sequences is accompanied by metabolic changes in the left hemisphere, regardless of the hand being used (Grafton et al. 2002).

Alternatively, ipsilateral left-hemisphere activity may occur preferentially for complex movements (i.e., movements that have a high degree of difficulty) but may not be specifically related to the sequential demands of the task. Behaviorally such complex movements can be characterized as actions that take longer to execute and/or show increased error rates compared with simpler movements.

To determine the specificity of this left-hemisphere response to ipsilateral actions, we used fMRI to assess cortical activity while participants performed various unimanual movements. In the first experiment participants were required to perform three movement patterns. One task required repetitive movements of a single finger. A second task required the production

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of movement sequences with four fingers. A third task was designed to match the sequence task in terms of complexity but lacked its sequential characteristics; each response consisted of a three-finger keypress, similar to the manner in which chords are played on the piano.

Most of the studies showing an asymmetry in ipsilateral recruitment have been restricted to right-handed participants (e.g., Kawashima et al. 1993; Kobayashi et al. 2003; Nikko et al. 2001). This raises the question whether this asymmetry reflects a preeminent role for the left hemisphere in motor control or whether they reflect a specific role of the hemisphere contralateral to the dominant hand in the control of both hands. While the apraxia literature would favor the former hypothesis (reviewed in Heilman 2000), the imaging results are mixed. Kim et al. (1993) reported that left-handed individuals also showed more ipsilateral activity during left-hand movements than during right-hand movements, albeit this difference was less clear than that observed for right-handers. Others, however, have reported a reversed pattern in left-handed individuals with ipsilateral activation most prevalent when the non-dominant, right hand was used (Kawashima et al. 1997) or symmetric bilateral activation for *both* left and right hand movements (Singh et al. 1998). This discrepancy in activation patterns for left-handed participants may partly result from the different movement tasks used in these studies. While Kim and colleagues (1993) and Singh et al. (1998) used sequential finger opposition movements, participants in the Kawashima et al. (1997) study performed simple finger tapping movements.

The following experiments were designed to investigate how ipsilateral activity in the motor cortex is affected by characteristics of the movement and the hand performing the action. Right- and left-handed participants were tested to further examine if asymmetric patterns of ipsilateral activation were related to handedness or hemispheric specialization.

Our primary focus in the present study is on activation patterns in the motor cortex as a function of movement type. However, the boundary in the precentral gyrus between the primary motor cortex and premotor cortex is difficult to define on a macroscopic level (for review, see Geyer et al. 2000). Identifying this boundary is especially problematic for the present purposes given that, as described in the preceding text, spatial representation of ipsilateral muscles is shifted in an anterior and ventral direction within the precentral gyrus (Cramer et al. 1999; Ziemann et al. 1999). The ipsilateral movement-related activity may be in the anterior extent of primary motor cortex or in the adjacent premotor region (see Rademacher et al. 2001). Indeed, the cytoarchitectonic differences between these two precentral gyrus regions are small, and in humans, functional distinctions have not been established (Geyer et al. 2000). Given these considerations, we will refer to activity across the precentral gyrus, as well as the anterior aspect of the central sulcus, as "motor cortex," acknowledging that the former is a composite of the anterior region of primary motor cortex and one of the premotor subareas. We return to this issue in the DISCUSSION.

In *experiment 1*, we found that the activity in the motor cortex was more pronounced for the sequential and chording tasks compared with the simple repetitive tapping task. Results for the sequence and chord conditions did not differ significantly from each other. Overall, these results are consistent with the hypothesis of a left hemisphere specialization for

complex actions rather than a specialization specific to sequential representations.

In our effort to create two types of complex movements, while keeping the difficulty of chord and sequence movements comparable, we had to introduce a number of other differences between the conditions. For example, both the chord and the sequence tasks required the recruitment and control of four fingers on each trial. In contrast, only a single finger was recruited on simple tapping trials. Thus the two complex tasks differ from the simple task in terms of the number of fingers (or muscles) that are required during a trial. Perhaps activation in the ipsilateral hemisphere is related to the number of recruited fingers (or muscles) rather than specific to the demands to link these fingers into a sequential pattern of movements or a configural hand posture.

We conducted a second experiment to evaluate this hypothesis. In separate blocks, participants performed repetitive tapping movements of either a single finger, two adjacent fingers or four adjacent fingers. By using synergistic combinations, we were able to manipulate the number of required fingers while minimizing the configural requirements for the movements. If the imaging results of *experiment 1* are related to the number of required fingers, then we should see an increase in ipsilateral activation across the one-, two-, and four-finger conditions respectively. We also included two sequence conditions, one in which the sequence was composed of four elements and a second in which the sequence was composed of six elements. Both are matched to the four-finger nonsequential task in terms of the number of required fingers. If the magnitude of the ipsilateral motor cortex response is related to movement complexity, then the extent of ipsilateral activation should be greater in the two sequencing tasks compared with the tapping conditions. Moreover, a comparison of the four- and six-element sequence conditions provides a strong test of this hypothesis because these two conditions are well matched in terms of kinematic requirements but differ in complexity.

To ensure that we obtained sufficient data for each condition in a single scanning session, we did not include the chord task in *experiment 2*. We also limited testing to right-handed individuals because the key question addressed here has to do with the definition of complexity rather than issues related to hemispheric asymmetries.

METHODS

Experiment 1

PARTICIPANTS. Eight right-handed (4 male, 4 female) and eight left-handed (4 male, 4 female) students from the University of California, Berkeley, were recruited and financially compensated for their participation. All participants were naive to the purpose of the study. Handedness was determined via a condensed version of the Edinburgh Handedness inventory (Oldfield 1971) and also assessed via multiple behavioral tasks reported elsewhere (Shannon et al. 2002). On a scale ranging from -2 (strong left-handed) to $+2$ (strong right-handed), the average score on the Edinburgh inventory was -0.97 (0.33 SD) for the left-handers and 1.24 (0.32 SD) for the right-handers. The protocol was approved by the Committee for the Protection of Human Subjects at UC, Berkeley.

APPARATUS AND STIMULI. Behavioral responses were recorded using custom-built five-key piano-style response boards made of non-ferrous materials. The thumb key for each board was longer than the

other keys so that participants could comfortably place their hands over all five keys. Diagnostic scans performed prior to this project confirmed that the devices did not introduce any artifacts into the MR signal. Stimulus presentation and recording of behavioral responses were controlled with E-Prime software (PST) run on a personal computer.

TASKS. Twenty-four hours prior to imaging, participants were trained on the three movement tasks. Participants were seated in front of a computer monitor and rested each hand on a response box. 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 (Fig. 1A). Five horizontal lines were displayed on the screen to represent the five fingers of the target hand. These lines were shifted $\sim 3^\circ$ to the left of center to indicate a left-hand trial and $\sim 3^\circ$ to the right of center to indicate a right-hand trial. The displace-

ment of the lines provided redundant information concerning the target hand and increased stimulus-response compatibility.

The *sequence* condition involved the cyclical production of a four-finger sequence. The digits 1- 4 appeared over four of the five lines, indicating the order in which the keys had to be pressed. Four different sequences were selected for each hand, and no sequence contained a "run" of three neighboring keys. The *chord* condition involved alternating between the designated chord and a single thumb response. The three fingers required for the chord were indicated by \times appearing above three of the lines. Participants were instructed to depress and release these three keys simultaneously. This response alternated with a single response produced by the thumb on the long key. Pilot work indicated that if only chord responses were required, participants would adopt the target hand configuration and make successive chord responses by wrist flexion and extension. The thumb response was used to ensure that participants would have to reconfigure the fingers prior to each chord response. Participants were instructed to minimize wrist movements when making all of the responses. Four of the 20 possible three-finger chords were selected, avoiding simple configurations with three adjacent depressed fingers. Finally, the simple *tap* condition involved repetitive tapping with a single finger. On these trials, a single \times appeared over one of the four lines, indicating the finger to be used.

The instruction screen remained visible for 2 s. After this, the screen was blank for an additional 2 s. During this period, participants were instructed to prepare the response while avoiding overt movements. Immediately after the preparation period, a green "GO" was displayed on the screen. Participants were instructed to produce the target movement as many times as possible within a 4 s movement period. Feedback was provided during training by transiently changing the color of the word GO to red whenever a wrong key was pressed. The word STOP indicated the end of the trial.

A block of trials consisted of eight sequence, eight chord, and four tap trials for each hand, presented in a random order. The number of successful repetitions for each movement type and the number of errors was reported at the end of each block. Participants completed 10 blocks of 20 trials during the training session.

The procedure was modified slightly during the imaging session. The duration of the preparation period, measured from the end of the instruction period to the onset of the imperative GO signal varied between 2 and 6 s. By varying the interval between the instruction- and delay-related activity on the blood-oxygenated-level-dependent (BOLD) response to the movements themselves (Dale 1999). Feedback within a trial was not provided during the imaging session, although overall performance feedback was given at the end of each block. Each movement condition was performed equally often during a scan, and the order was pr randomized to control for one-back order effects: each task was followed an equal number of times by each of the other tasks.

To ensure high proficiency during the imaging session, two sequence and two chord patterns were preselected for each hand. In addition, three practice blocks were run with the participants positioned in the scanner. Immediately thereafter, four test blocks of 48 trials were performed during image acquisition, resulting in a total run length of 8.5 min/block.

MRI ACQUISITION AND PROCESSING. A Varian 4T Unity INOVA scanner was used for the experiment. High-resolution gradient-echo (GEM) images were acquired along the axial plane as localizer images (18 slices, matrix size = 256×256 , thickness = 3 mm, gap = 0.5 mm). The field-of-view ($22.4 \times 22.4 \times 6.3$ cm) for these images encompassed all cortical regions above the Sylvian fissure. A total of 1,300 functional volumes were acquired across four consecutive scans using a Varian gradient echoplanar imaging (EPI) pulse sequence (18 slices interleaved, TR = 2,000 ms, TE = 28 ms, matrix size = 64×64 , thickness = 3 mm, gap = 0.5 mm, yielding isotropic voxels of

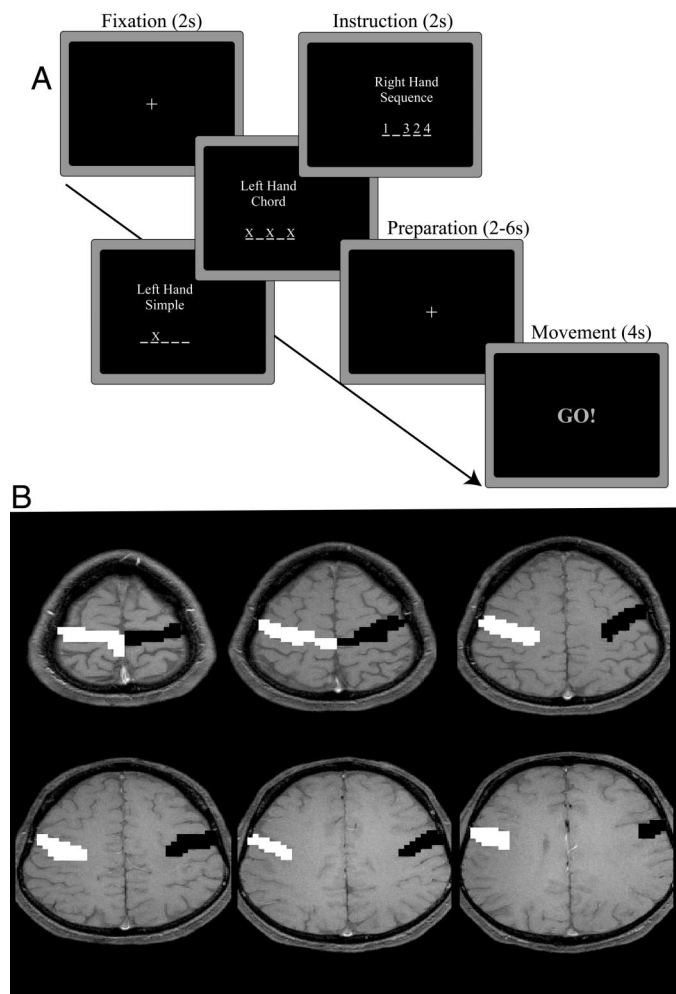


FIG. 1. A: timeline of events for each trial. After a 2 s fixation interval, an instruction cue was presented for 2 s, informing the participant of the required hand, movement condition, and specific pattern. After a variable preparation period, an imperative signal appeared, and participants were required to produce as many responses of the required pattern as possible during 4 s. All behavioral responses were made on a 5-key piano style response box. The thumb key was not used for either tapping or sequence movements. During chord movements, the participant alternated between producing the target chord and making a single response with the thumb on the 5th key. B: anatomically defined voxel maps of the left (white) and right (black) precentral gyrus from 6 slices of a GEM anatomical image in one individual. The precentral gyrus region of interest (ROI) spanned from 8 to 14 of the 18 total slices.

3.5-mm size) sensitive to 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. The angle and orientation of the functional slices were identical to those of the GEM images used for structural localization. For 12 of the participants, a high-resolution T1-weighted image was acquired using a FLASH pulse sequence (91 slices, matrix size = 91×109 , thickness = 2 mm). These images were later used for spatial normalization to determine the location of peak activation within each motor cortex (see following text).

DATA ANALYSIS. All functional images were realigned to the first image in the series to correct for rotation and translation of the participant's head during the scanning session. To correct for the temporal shift between slices due to the slice-acquisition sequence, every slice was realigned with linear interpolation to the beginning of each volume. VoxPrep software (Voxbo) was used to exclude voxels outside the parenchyma of the brain by thresholding. The time series for each voxel were high-pass filtered (cutoff frequency: 0.003 Hz) and analyzed using a modified general linear model (GLM) (see Friston et al. 1994) that takes into account the intrinsic autocovariance structure of the signal. Because this analysis focused on the average number of activated voxels in specified regions of interest, spatial smoothing was unnecessary, allowing more precise localization on an individual basis (see following text).

The independent variables for the GLM were delta functions for the instruction period, for the preparation period, and for the execution phase. For the latter two, a separate regressor was used for each of the six movement conditions (e.g., preparation of a right-hand sequence movement, or execution of a right-hand sequence movement). A separate regressor function was determined for the preparation period because it had the additional working memory component that was not present in the instruction phase.

The reference functions were convolved with an individual's hemodynamic response function (Aguirre et al. 1998) obtained in a separate scanning block. In this block, the hemodynamic response function was determined by having the participant repetitively press both thumb keys in response to a flashing visual stimulus. The stimulus was presented for 2 s with a varying interstimulus interval (range of 2–18 s). The participant was instructed to press as fast as possible during the 2-s stimulus epoch. Voxels in the motor cortex were identified bilaterally, and the averaged, time-locked BOLD response to the stimulus (and responses) was estimated for each subject.

For each regressor, a regression-coefficient (β) was estimated for each voxel and saved in a separate whole-brain voxel map for later analysis. The within-block trial order was determined a priori as to minimize the correlation between the different regressors for each condition. This method used an iterative randomization routine to identify trial sequences that minimized off-diagonal values in the design matrix used in the GLM processing, thus optimizing efficiency (Dale 1999). The resulting correlation between the regressors for the preparation and execution periods was 0.22 for each condition. Four sets of these optimal trial sequences were generated for each subject.

A within-subject region of interest (ROI) approach was used to evaluate asymmetric activation of cortical regions given various concerns about averaging across individuals. Group analyses of fMRI data typically involves high-dimensional warping to fit individual brain and activation maps to a reference brain (Friston et al. 1995). Because the spatial localization of ipsilateral activity may be more variable between individuals than contralateral activity, spatial normalization and subsequent group analyses may lead to an underestimation of the ipsilateral activity (Nirko et al. 2001). Furthermore, given local structural variability between individuals, a high dimensional warp does not produce exact alignment of the central and

precentral sulci.¹ Spatially aligned and averaged group data for the precentral gyrus would likely consist of a mixture of activation from pre- and postcentral gyrus as well as adjacent frontal regions. Given these considerations, region masks were generated on the localizer GEM images for each participant (Fig. 1B). ROI maps were drawn for the left and right precentral gyrus, using the most superior slice down to the first slice where the lateral fissure was present. This region spanned the entire surface of the precentral gyrus and the anterior bank of the central sulcus to include the entire motor cortex. Additional maps were generated for adjacent frontal regions using the same set of slices. The posterior boundary began at the anterior bank of the precentral sulcus and extended ~ 10.5 –28 mm (3–8 voxels) in the anterior direction (superior and medial frontal gyri). This axial distance was liberally estimated so as to cover the complete extent of the dorsal premotor region and part of the ventral premotor region (Shubotz and von Cramon 2003; Talairach and Tournoux 1988).

As stated previously, the voxel-by-voxel regression coefficients (β) for each trial phase and movement condition were determined using a GLM. Significantly activated voxels within the ROI were defined as those showing higher activation during the movement phase for a given movement condition compared with rest with the statistical criterion set to $t = \hat{\beta}/SE(\hat{\beta}) > 2.75$. This threshold corresponds approximately to an α estimate of <0.005 . The number of super-threshold voxels (N) was used as a measure of the extent of activation within each region, and these estimates were submitted to a group analysis. In addition to the extent of activation within an ROI, a trial-averaged BOLD response (percentage signal change) was determined for the activated voxels. For individual participants, there were slight differences in the size of the left and right motor cortex maps. However this difference was not significant for the group as a whole [394 vs. 412 voxels, $t(15) = 1.16$, $P = 0.261$].

To compare the amount of ipsilateral activity across participants and tasks while taking into account the level of overall activation, we normalized the number of activated voxels in the ipsilateral cortex (N_{ipsi}) by the total number activated in the contralateral (N_{contra}) and ipsilateral motor area

$$I = \frac{N_{\text{ipsi}}}{N_{\text{contra}} + N_{\text{ipsi}}}$$

Separate scores were computed for left- and right-hand movements for each task. This score can range from 0 (no ipsilateral activation) to 1 (all ipsilateral activation) with scores <0.50 corresponding to conditions in which the number of voxels activated in the contralateral hemisphere are greater than in the ipsilateral hemisphere.

As a measure of hemispheric asymmetry (HA) we computed the difference in the relative ipsilateral activation of left and right hand movements

$$HA = I_{\text{LeftMovement}} - I_{\text{RightMovement}}$$

Thus positive HA scores correspond to situations in which the left hemisphere (during left-hand movements) shows more ipsilateral activity than the right hemisphere (during right-hand movements). Negative HA scores would correspond to the reverse situation.

In addition to functional brain asymmetries, we also determined behavioral asymmetries by comparing the performance of left and right hand. As a raw-performance score, we used the total number of correct movements (M) made during each trial. For each movement condition, a normalized measure of behavioral asymmetry (BA) was computed as

¹ We tested this by spatially normalizing each individual's brain to the MNI brain, including the ROI map for the left and the right motor cortex using the SPM 99 algorithm. For the 12 participants, the anterior boundary of the motor cortex at the height of the junction of superior frontal and prefrontal sulcus varied between -10 and -24 mm in anterior-posterior direction (the MNI templates anterior border is at -16 mm).

$$BA = \frac{M_{\text{RightHand}} - M_{\text{LeftHand}}}{M_{\text{RightHand}} + M_{\text{LeftHand}}}$$

Positive scores indicate that the participant was able to produce more right-hand movements than left-hand movements within the time allowed.

Previous studies have reported that the area of maximal activation in the precentral gyrus during ipsilateral hand movements is lateral and ventral to the area of maximal activation during contralateral movements (Cramer et al.1999; Ziemann et al. 1999). To determine the correspondence of activation within the motor cortex for contralateral and ipsilateral movements, we identified the location of maximal activation. This maximum was identified on a smoothed *t*-map (FWHM = 8 mm) within the ROI mask using established algorithms for identifying local maxima (SPM99). When multiple clusters of task-related voxels were identified, only the location of the voxel with the greatest *t*-value was used. We estimated the direction and magnitude of spatial shifts between the contra- and ipsilateral conditions on spatially normalized *t*-maps to make the results comparable across participants. For this normalization, we used a 7 × 8 × 7 parameter nonlinear transform (SPM99) (Friston 1995) to warp the individual anatomical T1 images onto the MNI template. The individual ROI maps were also normalized using the same procedure and used as masks for analysis.

To further improve local alignment within the motor cortex, the coordinates of these voxels were expressed relative to the coordinates of the hand notch on the anterior bank of the precentral gyrus, marked on each individual brain. The *x*, *y*, and *z* components of the spatial shift of peak activation between ipsi- and contralateral hand movements were then submitted to a MANOVA with group as a factor, separately for each hemisphere. The intercept term of the MANOVA provides a test of whether there was a directionally consistent shift across all individuals, while the group effect examines whether this shift was different between right- and left-handed participants.

Experiment 2

PARTICIPANTS. Eight right-handed participants (4 male, 4 female) were recruited from the University of California Berkeley population. They were financially compensated for their time. The mean handedness score for this group was 1.6 ± 0.23 (SD). The secondary handedness assessments were not performed on this group. Due to movement related artifacts (see following text), we could not use the data from two subjects, leaving a total of six participants in the analyses. The participants included one of the authors (T. Verstynen).

PROCEDURE. To increase the statistical power for finding task-related voxels, we switched from an event-related to a block design. At the start of each block, the participant was cued to produce one of five possible movements. The *one-finger tapping* movements were cued as previously described. The *two-* and *four-finger tapping* movements were cued by the presentation of adjacent × over the lines corresponding to the target fingers. To include combinations that seemed naturally synergistic, the ring/pinky finger combination was excluded from the two-finger condition. The cues for both of the sequence conditions were identical to that used in the sequence condition in the preceding text. To provide a strong contrast of the two sequence conditions, the *sequence easy* condition included sequences consisting of ascending (index, middle, ring, then pinky) or descending (pinky, ring, middle, then index) runs. For the *sequence difficult*, a second set of lines representing the finger locations was drawn below the original array. Positions for the first four finger movements were displayed in similar fashion as the simple sequence condition. The fifth and sixth keypresses of the sequence were cued on the corresponding finger locations on the second row of lines. Four possible six-element sequences were used, all selected so as not to include three or more consecutive presses of neighboring fingers.

Unlike *experiment 1*, all sequences excluded the use of the thumb. The sequences were designed so that, across the experiment, all four remaining fingers were used an equal number of times.

The instruction screen remained visible for 2 s. Immediately after this, the word “GO” was presented in green in the center of the screen to indicate the start of the movement period. This period lasted for 16 s, and participants were instructed to produce as many movements as possible at a fast but comfortable pace. In contrast to *experiment 1*, during this epoch the cue indicating the target hand and the specific finger configuration remained visible on the screen. A rest period of either 8 s (training blocks) or 16 s (scanning blocks) separated each block.

As before, participants were trained to make all responses by flexing and extending their fingers and to minimize movements of the wrist. Thumb movements were excluded from all of the conditions. Participants were trained on two specific movement patterns within each condition, except the four-finger tapping condition which has only one possible pattern. As with *experiment 1* only during training would the imperative stimulus turn red whenever an erroneous key-press was detected. Feedback was provided at the end of the block during both the training and scanning blocks.

MRI ACQUISITION AND DATA ANALYSIS. MRI acquisition parameters were identical to those used in *experiment 1*. A total of 1,296 functional images were acquired over eight separate scanning runs, each lasting 324 s. One pattern from each movement condition was performed during an individual scanning run. The order of presentation for each trial type was randomized within an individual run. Rather than using empirically derived hemodynamic response functions (HRF) to convolve with the hypothetical regressor functions, we employed the SPM canonical HRF. Individual differences in the HRF have minimal effect on the analysis of data from block designs.

Two participants had to be excluded from all analyses due to significant movement related artifacts in the EPI images.

RESULTS

Experiment 1: Is ipsilateral activation specific to sequential movements?

BEHAVIORAL RESULTS. Behavioral performance, assessed as the average number of correct responses for each movement pattern for the training and imaging sessions, is shown in Table 1.

First, there were significant differences between the three tasks in the number of responses produced during the training [$F(2,28) = 134.17, P < 0.001$] and imaging [$F(2,28) = 72.41, P < 0.001$] sessions. As expected, the tapping task resulted in more correct responses than the sequence and the chord condition, indicating that this task was indeed the least difficult of the three tasks. Participants also made more responses in the sequence condition than in the chord condition, a finding that might suggest that the chord task was harder than the sequence task; however, successful responses for the chord task consisted of alternating between the three-key chords and the single thumb press, whereas each individual key press in the sequence task was counted as a successful response. As an alternative measure of complexity we considered the error rate for each task. While participants made marginally more errors in the sequence (5.4%) than in the chord condition during training [4.2%; $F(1,14) = 4.04, P = 0.064$], this effect disappeared during imaging [$F(1,14) = 2.87, P = 0.112$]. In comparison, the error rate in the tap condition was 0.2%. Thus our data suggest that the two complex tasks were roughly matched for difficulty, at least after the initial training.

TABLE 1. Correct movements in the 4–5 response period

	Sequences		Chords		Tapping	
	Left handers	Right handers	Left handers	Right handers	Left handers	Right handers
Training						
Left hand	14.53 ± 1.09	13.77 ± 1.07	10.13 ± 0.77	11.25 ± 1.20	21.30 ± 1.47	19.01 ± 1.23
Right hand	14.42 ± 1.16	14.79 ± 0.99	10.55 ± 0.95	11.98 ± 1.29	21.16 ± 1.10	21.59 ± 1.28
BA score	−0.57 ± 0.85	3.67 ± 1.12	1.63 ± 1.22	2.95 ± 2.06	−0.06 ± 2.11	6.47 ± 1.69
Imaging						
Left hand	13.57 ± 1.01	15.87 ± 1.71	10.85 ± 0.77	12.88 ± 1.60	21.50 ± 1.45	20.47 ± 1.01
Right hand	15.17 ± 1.44	16.96 ± 1.73	11.05 ± 0.95	14.05 ± 1.67	19.56 ± 1.07	21.25 ± 1.10
BA score	5.02 ± 2.13	3.55 ± 2.41	0.47 ± 2.31	4.56 ± 1.19	−2.06 ± 2.36	4.22 ± 1.87

Mean number of correct movements produced within the 4 s response period ± (SE) estimates when using either the left or right hand and the resulting behavioral asymmetry (BA) values (see text for details of the BA calculation).

Both right- and left-handed people were equally capable at performing the tasks, with no group differences in either the average number of responses nor error rates [all: $F(1,14) < 1$]. There were, however, significant differences between the two groups in the pattern of performance for the three tasks. Overall, right-handed persons were more proficient when using their dominant hand for all three types of movements (all 1-sample t -test > 2.06). In contrast, a dominant hand advantage was only evident for left-handed people during the simple tapping task in the imaging session. For the two more complex tasks, the left-handed people tended to exhibit symmetric performance for the two hands. In fact, during the imaging session, the left-handed persons made more sequential responses when performing with the nondominant, right hand compared with the dominant, left hand ($P < 0.005$).

ACTIVATION AND LATERALIZATION OF THE MOTOR CORTEX. As expected, the level of activation within the precentral gyrus mask increased with movement complexity. More precentral voxels showed significant activation in the sequence and chord tasks than during tapping [task: $F(2,28) = 20.70$, $P < 0.001$; Fig. 2A].

In all three tasks, activity was greater in the contralateral hemisphere compared with the ipsilateral hemisphere. This was observed for both right- and left-handed people, resulting in ipsilateral (I) scores consistently > 0.5 (Fig. 2B). However, all I scores were > 0 , indicating that there was significant ipsilateral activation for all movements. The strength of this activation differed significantly between movement conditions [task: $F(2,28) = 20.59$, $P < 0.001$]. Post hoc comparisons indicated that sequence and chord movements led to a higher proportion of ipsilateral activity than simple key taps. Thus when the number of ipsilaterally activated voxels was normalized by the total number of activated voxels in both the left and right motor regions, we observed a greater ipsilateral response during complex tasks. In other words, the increased overall activation during complex movements was especially pronounced in the hemisphere ipsilateral to the moving hand. The magnitude of these I scores was not different between left- and right-handed people [group: $F(1,14) < 1$].

The sequence condition was similar to tasks used in previous imaging studies (Kawashima et al. 1993; Kim et al. 1993; Singh et al. 1998). Similar to what was reported in those studies, we found that right-handed participants had more ipsilateral movement-related activity when using the left hand. Specifically, their I scores were significantly larger when the sequences were produced by the left hand compared with the right hand [$t(7) = 3.43$, $P = 0.011$].

To examine whether this effect was specific to sequential finger movements, we performed a similar analysis on the other two movement tasks. The results for the chord condition were essentially identical to those observed in the sequence task: left-hand chords resulted in more ipsilateral activation than right-hand chords [$t(7) = 2.73$, $P = 0.029$]. The ipsilateral activity for the key tapping condition, although reduced compared with the complex tasks, was also significantly different between the two hemispheres [$t(7) = 4.82$, $P = 0.002$], with left finger taps resulting in more ipsilateral activation than right finger taps. Thus for right-handed people, ipsilateral activation is more pronounced when they use their nondominant left hand for variety of movement tasks.

The inclusion of left-handed participants allowed us to assess whether patterns of ipsilateral activation are related to handedness, reflect a special role of the left hemisphere in complex movements, or both. As with right-handed participants, the left-handed group also showed a significant effect of movement condition [$F(2,14) = 4.08$, $P = 0.04$], reflecting greater ipsilateral activity during complex movements. Comparing the average I scores for movements of the left versus the right hand indicated slightly stronger ipsilateral activity in the left hemisphere: e.g., I scores were slightly higher during left-hand movements. However, the distribution of I scores for the left-handed people was more variable, and the hand effect did not approach significance for any of the three tasks [sequence: $t(7) = 0.72$, $P = 0.49$; chord: $t(7) = 0.46$, $P = 0.66$; tap: $t(7) = 0.54$, $P = 0.60$].

Figure 3 shows the joint distributions of Hemispheric Asymmetry (HA) scores for each pair of movement conditions. The hypothesis that increased ipsilateral activity is related to the frequency of hand use (i.e., handedness) in everyday behavior would predict that the left-handed group would exhibit a mirror reversal of HA-scores compared with the right-handed participants. This was clearly not the case for complex movements. The HA scores for the chord and sequence movements were closely related to each other, even after accounting for handedness (partial $r = 0.807$). While the population of right-handed participants (○) clusters consistently in the upper right hand quadrant, indicating more ipsilateral activity in the left hemisphere, the scores for the left handed people (●) are more dispersed. Interestingly, only one left-handed participant showed a mirror-reversed pattern of the HA scores for both complex tasks, reflecting greater ipsilateral activity in the right than in the left hemisphere. In contrast, during simple movements, half the left-handed participants showed such a reversal,

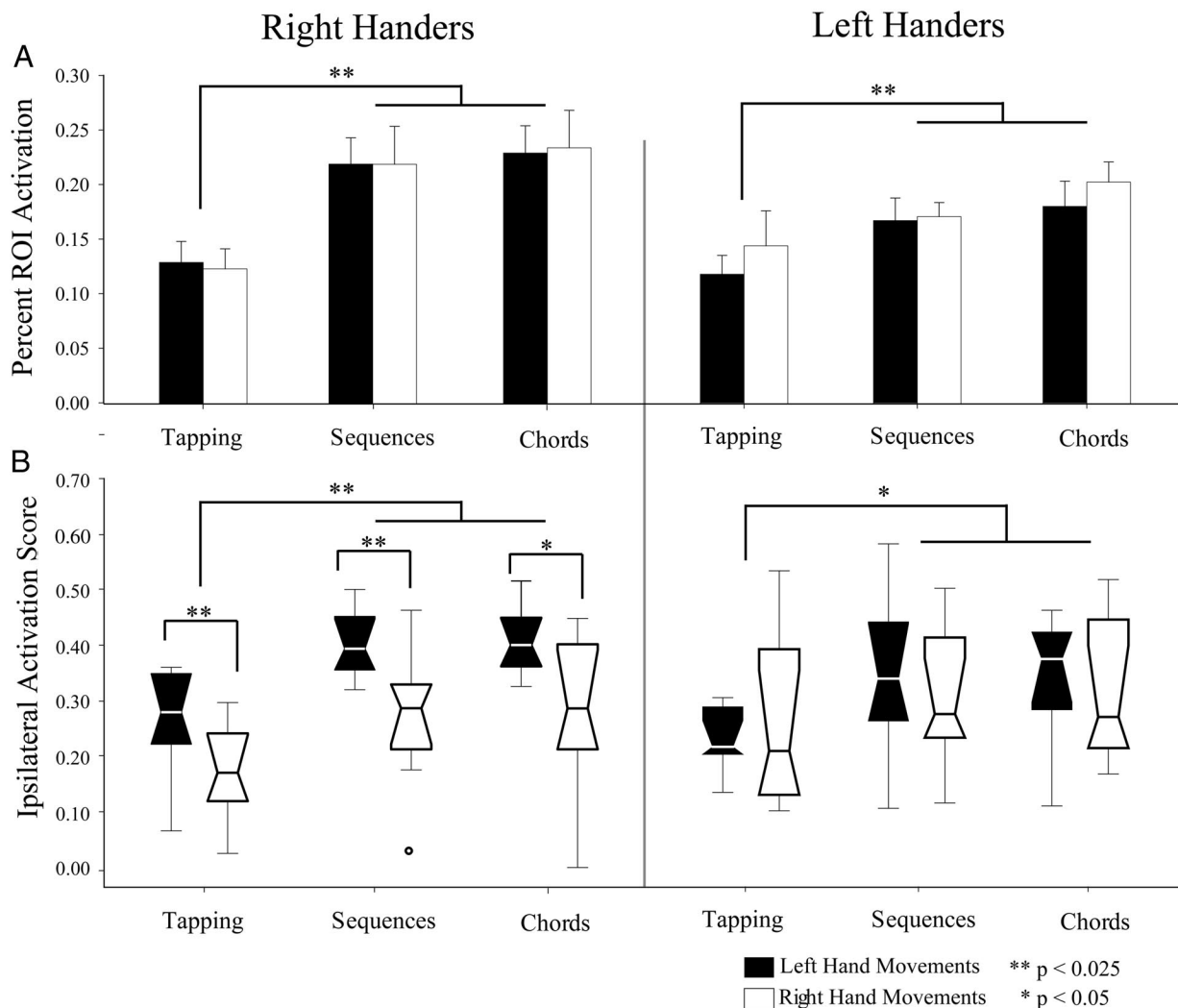


FIG. 2. A: percent of voxels activated within both the ipsi- and contralateral motor cortices during all 3 movement conditions and for both left- and right-hand movements. In both groups, sequence and chord tasks resulted in more activation than the simple key tapping task. B: ipsilateral activation coefficients for the precentral gyrus during tapping, sequence, and chord movement conditions. Values are presented as a ratio of ipsilateral activation to overall activation. Distributions of values are presented as Tukey box plots where the upper and lower bounds of the boxes represent the 95% confidence intervals and the error bars represent the range of all values in the group. For tapping movements, there was less ipsilateral activity than for sequence and chord movements. In right-handed people, there was considerably more ipsilateral activation for left- than for right-hand movements. Although a similar pattern of mean scores was present for the left-handed people in the 2 complex conditions, the effect of hand was not significant for any of the 3 tasks.

resulting in a marginally significant group difference, $t(14) = -2.06, P = 0.058$. In summary, while left-handed persons showed a much more variable asymmetry pattern compared with right-handed people, they also tended to preferentially recruit the left hemisphere for complex movements.

SPATIAL CHARACTERISTICS OF PRECENTRAL ACTIVATION. Previous studies have suggested that the center of activation within the precentral gyrus differs for contra- and ipsilateral hand movements (Cramer et al. 1999; Ziemann et al. 1999). To examine this issue in the current study, we identified the center of peak activation within the motor cortex of each hemisphere.² Given the similarities in the pattern of ipsilateral activation for the two complex tasks, the data from the sequence and chord conditions were combined to produce a composite activation map for the two types of complex movements.

Consistent with the results of previous studies, the center of activation for the ipsilateral movements was shifted in an anterior, ventral, and lateral direction from the center of activation for contralateral movements (Fig. 4). The average shift was 24 mm (12 voxels at 2 mm³; 6 voxels anterior, 6 voxels ventral, and 5 voxels lateral). The shift was consistent across individuals and was significant for both the left (Hotelling's Trace = 3.23, $P = 0.007$) and right (Hotelling's Trace = 2.86, $P = 0.019$) hemispheres. There was no significant difference in the direction or magnitude of the shift between the left- and right-handed people, in either the left (Hotelling's Trace = 0.50, $P = 0.33$) or right hemisphere (Hotelling's Trace = 1.22, $P = 0.114$).

TEMPORAL CHARACTERISTICS OF MOTOR CORTEX ACTIVATION. Using an event-related fMRI design allowed us to investigate the temporal features of contra- and ipsilateral activation. Note that the center of activation for ipsilateral

² Spatial analyses were limited to the 12 participants (6 right-handed, 6 left-handed) for whom high resolution T1 images were acquired.

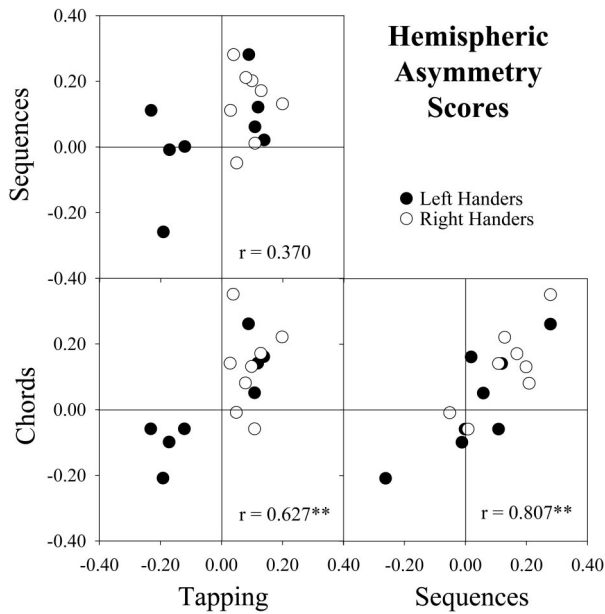


FIG. 3. Joint distributions of Hemispheric Asymmetry (HA) scores for the 3 movement conditions. Right-handed participants (\circ) showed consistent asymmetries, indicated by a higher degree of ipsilateral activation in the left hemisphere (positive HA scores). The left-handed group (\bullet) exhibited a broader range of values. The partial correlation coefficients (after accounting for the effect of handedness) indicated that the HAs were closely related in the 2 complex tasks but to a lesser degree between each complex and the simple tapping task.

movements is more likely to be in premotor cortex than in the primary motor cortex (Geyer et al. 2000). This raises the possibility that ipsilateral activation may be especially prominent during movement preparation, whereas contralateral activation would be especially prominent during movement execution (or both preparation and execution). This hypothesis predicts that the time course of activation should be different for ipsi- versus contralateral movements. However, the temporal profile of the activation functions were remarkably similar for ipsilateral and contralateral movements (Fig. 5). To assess these functions statistically, we fit a reference function to the

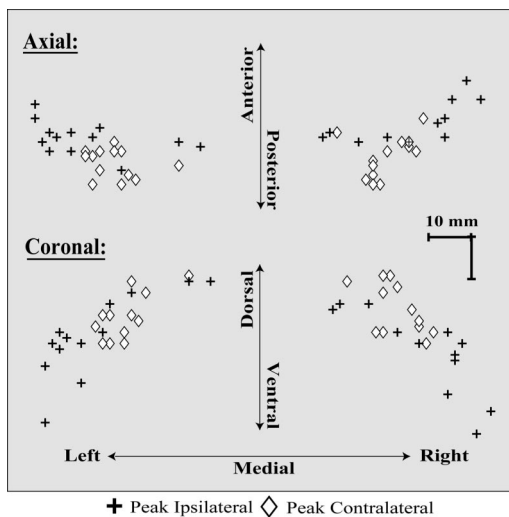


FIG. 4. Location of peak activation during contralateral (\diamond) and ipsilateral ($+$) complex movements. The sites of activation for ipsilateral movements shift ventrally, laterally, and anteriorly relative to those for contralateral movements.

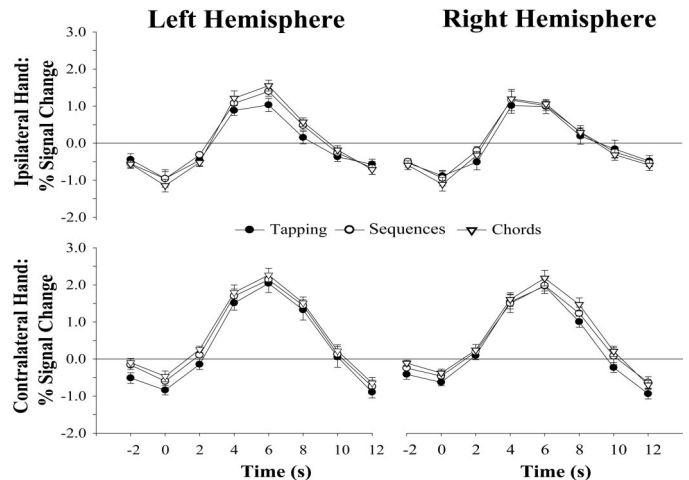


FIG. 5. Mean time series of normalized blood-oxygen-level-dependent (BOLD) responses, averaged over all significantly activated voxels in each hemisphere, calculated separately for ipsilateral (*top*) and contralateral (*bottom*) movements during the 3 movement tasks. The imperative signal appeared at time 0 and the signal to end movement appeared 4 s later. Higher peak activation is observed in the left hemisphere during ipsilateral movements on the sequence and chord tasks. The time courses for ipsi- and contralateral activation are comparable and are execution related. The functions start <0 because percent signal change is expressed relative to the average signal over the whole time series.

time course of the BOLD response for each individual hemisphere and hand.³ The reference function consisted of a 4 s boxcar function, convolved with an assumed HRF response function (composed of 2 overlaid gamma functions) (for details, see Aguirre et al. 1998). We used a least-square estimation procedure with two free parameters for overall response amplitude (an additive shift term and a multiplicative scale term, both in the y direction) and one parameter for time shift. The parameter estimates for the time shift were submitted to a group \times condition \times hemisphere \times hand ANOVA. None of the main effects or interaction terms were significant (all P s > 0.08). In particular, the hemisphere \times hand interaction was not significant [$F(1,13) = 2.92, P = 0.11$], indicating that no gross differences existed between the temporal profile of ipsi- and contralateral activation.

CORRELATION OF NEURAL AND BEHAVIORAL ASYMMETRIES. To investigate the degree that the behavioral and physiological measures of left/right asymmetries relate to each other, we first looked at the correlation between hemispheric asymmetries (HA) and the strength of handedness as measured by the Edinburgh inventory.

The Edinburgh score clearly separated the left- and right-handed people into two distinct groups (Fig. 6A). However, the strength of the hand preference within each group was not related to asymmetries in brain responses. When we partialled out the effect of handedness, the correlations between the Edinburgh score with the HA measure were not significant.

We next asked whether asymmetries in brain responses related to the measures of behavioral performance on our experimental tasks. That is, do people who show more lateralized ipsilateral activation have more of a performance dif-

³ The temporal analysis could not be performed on one right-handed participant, because a data file for this participant was corrupted.

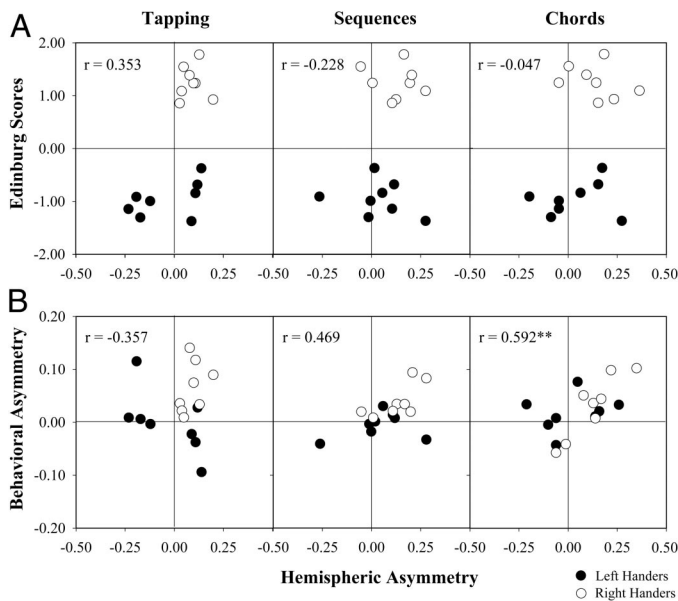


FIG. 6. A: correlations between scores on the Edinburgh Handedness inventory and hemispheric asymmetry (HA) scores. Positive Edinburgh scores indicate an increased preference for using the right hand in everyday activities, whereas negative scores indicate a preference to use the left hand. Positive HA scores indicate greater ipsilateral activation in the left hemisphere, negative scores indicate greater ipsilateral activation in the right hemisphere, and zero corresponds to symmetric ipsilateral activation. There was no significant relationship between hand preference and hemispheric asymmetries in any of the 3 movement conditions. Partial correlation coefficients (accounted for handedness) are reported. B: Relationship between measures of behavioral asymmetry (BA) and HA scores. Positive BA scores indicate better performance with the right hand. The 2 measures are significantly correlated (after accounting for the effects of handedness) for the chord task and marginally significant for the sequence task. However, no relationship is apparent in the tapping task.

ference between the hands than people who show a less pronounced pattern of asymmetry? To answer this question, we examined the correlations between the HA and BA scores (see METHODS). Across both groups, individual BA scores were significantly correlated between imaging and training sessions for the simple task, $r_{\text{Simple}} = 0.640, P = 0.008$, and the chord task, $r_{\text{Chords}} = 0.508, P = 0.045$. This, however, was not true for the sequence task, $r_{\text{Sequence}} = 0.08, P = 0.768$, because of the right-hand advantage observed in left-handed participants during the scanning session. Given the inconsistency in the BA scores for the sequence task and the fact that the behavioral data from the scanning session were more variable, the BA scores were based on performance during training session only.

Figure 6B shows a relatively close relationship between the behavioral and hemispheric measures of asymmetries for the two complex tasks but not for tapping movements. After removing the effect of handedness, there was a significant correlation between HA and BA scores for the chord movements ($r = 0.592, P = 0.020$) and a marginal relationship for the sequence task ($r = 0.469, P = 0.078$). The relation was not present for tapping movements ($r = -0.357, P = 0.192$).⁴

In summary, asymmetries of motor cortex activation were not related to the degree of handedness as determined by a

⁴ None of the behavioral asymmetry measures correlated with scores on the Edinburgh handedness inventory (all $P > 0.50$ from partial correlation coefficients), indicating that there may be a discrepancy between hand preference and ability.

standard behavioral assessment instrument. However, the activation patterns were related to intermanual performance differences during complex movements. The difference of ipsilateral activation between the two hemispheres was greater in those individuals who showed a bigger difference in performance between the two hands. Specifically, the lower the relative proficiency of a hand was, the greater the amount of activity elicited in the ipsilateral motor region. Participants that exhibited a stronger left-hand disadvantage for complex movements showed a greater recruitment of the left hemisphere during these actions.

ACTIVATION AND LATERALIZATION OF ADJACENT FRONTAL REGIONS. Activation patterns observed in ipsilateral motor cortex, especially during complex left-hand movements, may also be manifest in neural regions higher up in the motor hierarchy. To investigate this issue, we performed the same analysis on voxel masks that encompassed frontal regions adjacent to precentral gyrus and included most of the dorsal and part of the ventral premotor cortices. In general, these regions had far fewer task-related voxels for a given movement compared with the motor cortex (see Table 2). As a result, the *I* scores for this region were much more variable. Nonetheless, it is immediately apparent that the *I* scores in the frontal regions were much higher than in the motor cortex [$F(1,14) = 68.23, P < 0.001$], indicating more bilateral activation across all conditions. Similar to what was observed in the motor cortex, right-handed participants had significantly greater ipsilateral responses during left-hand movements [hand: $F(1,7) = 9.23, P = 0.019$]; however, unlike the motor cortex, this ipsilateral response was expressed equivalently across all movement conditions [task: $F(2,14) < 1$], regardless of which hand was used [task \times hand: $F(2,14) < 1$]. In left-handed participants, *I* scores were not significantly influenced by hand [$F(1,7) < 1$] or movement condition [task: $F(2,14) < 1$]. For this group, a marginally significant interaction was observed between moving hand and movement type [$F(2,14) = 3.54, P = 0.057$], reflecting greater ipsilateral responses to simple key tapping than sequence and chord movements.

TABLE 2. Grouped lateralization and percent ROI activation scores for the frontal, premotor region

	Tapping	Sequences	Chords
Left handers			
Left hand			
<i>I</i> score	0.55 ± 0.09	0.42 ± 0.06	0.42 ± 0.04
Activation	0.05 ± 0.13	0.08 ± 0.01	0.07 ± 0.01
Right hand			
<i>I</i> score	0.39 ± 0.07	0.51 ± 0.06	0.41 ± 0.08
Activation	0.06 ± 0.03	0.07 ± 0.01	0.06 ± 0.01
Right handers			
Left hand			
<i>I</i> score	0.54 ± 0.07	0.49 ± 0.03	0.53 ± 0.03
Activation	0.05 ± 0.01	0.10 ± 0.01	0.09 ± 0.01
Right hand			
<i>I</i> score	0.36 ± 0.05	0.38 ± 0.05	0.39 ± 0.05
Activation	0.04 ± 0.01	0.10 ± 0.03	0.08 ± 0.02

Values are mean ± SE. Overall there were fewer suprathreshold voxels in this region compared to the motor cortex region of interest (ROI). However, the *I* scores were consistently higher. While right-handed participants appear to have greater ipsilateral premotor recruitment during left-hand movements, the degree of this response is not modified by movement type. This asymmetry was not observed in left-handed participants.

In summary, the results show that for these frontal, primarily premotor areas, the activation was more bilateral than that found in motor cortex. Moreover, the degree of activation during ipsilateral movements was relatively independent of task complexity. For right-handed people, the disproportionate engagement of the left hemisphere during ipsilateral movements is found in both the motor and frontal regions. This effect was present in all three movement conditions. In left-handed people, hemispheric asymmetries observed during ipsilateral movements tend to decrease for more complex movements. Based on these results it appears that frontal regions anterior to the precentral gyrus share the same hand-specific asymmetry, but the task-specific increase in ipsilateral activity is not shared between the two regions. Thus it is unlikely that this complexity effect in motor cortex reflects an "overflow" of activity from premotor cortices in adjacent frontal regions. Given the small amount of suprathreshold premotor voxels, however, these results should be interpreted with caution.

Experiment 2: Is ipsilateral activation a function of the number of required fingers?

BEHAVIORAL RESULTS. We observed a significant effect of movement condition on the number of correct keypresses made during training [$F(4,20) = 26.88, P < 0.001$] and imaging [$F(4,20) = 18.84, P < 0.001$] sessions. Post hoc analysis revealed that both sequence movements resulted in the fewest number of correct keypresses (see Table 3). This is consistent with the implication that these movements are more complex than the tapping movements.

The BA scores (Table 3) were significantly positive [training: $F(1,5) = 10.86, P = 0.022$, imaging: $F(1,5) = 19.06, P = 0.007$], indicating better performance with the dominant, right hand compared with the nondominant, left hand across all conditions. No significant difference between conditions was observed in the asymmetry during imaging [$F(1,5) = 0.40, P = 0.80$], but we did find significant difference during training [$F(1,5) = 3.12, P = 0.038$]. As in *experiment 1*, the BA scores were higher during tapping movements than during the sequence condition.

The error data yielded similar trends. Essentially no errors were observed in the three tapping conditions. This reinforces our assumption that these movements were very easy. Error rates were higher in the sequence conditions (1.4 and 1.5% for the easy and hard conditions, respectively) with similar values for the left (1.6%) and right (1.3%) hands, $F(1,5) < 1$.

ACTIVATION AND LATERALIZATION OF THE MOTOR CORTEX. As in *experiment 1*, activation in the motor cortex was not directly related to the number of keypresses. Instead, the two sequence conditions resulted in significantly more activation than the three tap conditions [task: $F(4,20) = 9.02, P < 0.001$] despite the fact that the fewest responses were recorded in this condition. As shown in Fig. 7A, the number of suprathreshold voxels during the sequential conditions was greater than the tapping condition that involved the same number of fingers (4-finger simple). While there was no overall difference between right- and left-hand movements [hand: $F(1,5) = 1.69, P = 0.251$], the task \times hand interaction showed a non-significant trend [$F(4,20) = 2.50, P = 0.075$]. The increase of activation with movement complexity appears to be especially pronounced during left-hand movements. In sum, these results suggest that responses in the motor cortex are more strongly linked to the complexity of a movement pattern (i.e., sequential movements) rather than the number of recruited fingers or speed of the movements.

We next turn to the proportion of ipsilateral activity (*I* scores, Fig. 7B). First, there was a main effect of task [$F(4,20) = 9.05, P < 0.001$]. Post hoc comparisons suggest that ipsilateral responses were greater during the two sequence conditions compared with the tapping conditions (all P s < 0.004), whereas the tapping conditions did not differ from each other (all P s > 0.35). We also found a trend for more ipsilateral activation in the sequence-difficult than in the sequence-easy condition [$t(5) = 2.24, P = 0.075$]. Thus the amount of ipsilateral activation does not depend on the number of fingers involved in the task but rather depends on the complexity of the task.

In terms of ipsilateral activation, the main effect of hand was significant, [$F(1,5) = 10.33, P = 0.024$] as was the hand by task interaction [$F(4,20) = 5.32, P = 0.004$]. Post hoc comparisons indicated that the increase in ipsilateral motor cortex activity for the two sequence conditions was most pronounced during left-hand movements. This asymmetry was not observed during the three tapping conditions regardless of the number of fingers involved in the movement.

These results clearly indicate that both the degree and asymmetry of ipsilateral responses to left- and right-hand movements is not related to the fact that these tasks required the control of more fingers. Rather, this pattern seems to emerge when the coordination requirements becomes more complex either through the demands of planning and/or exe-

TABLE 3. Behavioral responses (mean number of movements and behavioral asymmetry scores) for experiment 2

	Tapping:			Sequence:	
	1-Finger	2-Finger	4-Finger	Easy	Difficult
Training					
Left hand	74.78 \pm 4.16	69.48 \pm 2.99	57.31 \pm 2.80	56.32 \pm 4.50	44.39 \pm 5.40
Right hand	77.06 \pm 4.41	73.94 \pm 5.60	61.03 \pm 3.77	56.67 \pm 4.98	43.32 \pm 4.87
BA score	1.48 \pm 1.24	2.62 \pm 2.03	2.96 \pm 2.74	0.15 \pm 1.51	-0.96 \pm 2.37
Imaging					
Left hand	79.05 \pm 4.39	78.00 \pm 3.54	65.61 \pm 4.32	58.66 \pm 4.25	49.77 \pm 3.69
Right hand	85.61 \pm 3.95	80.82 \pm 4.88	69.32 \pm 4.85	63.28 \pm 4.68	52.12 \pm 4.70
BA score	4.09 \pm 1.87	1.55 \pm 1.89	2.71 \pm 1.18	3.82 \pm 1.76	1.91 \pm 1.76

Values are mean \pm SE. Overall, the participants executed more movements in the three tapping conditions than either sequence condition.

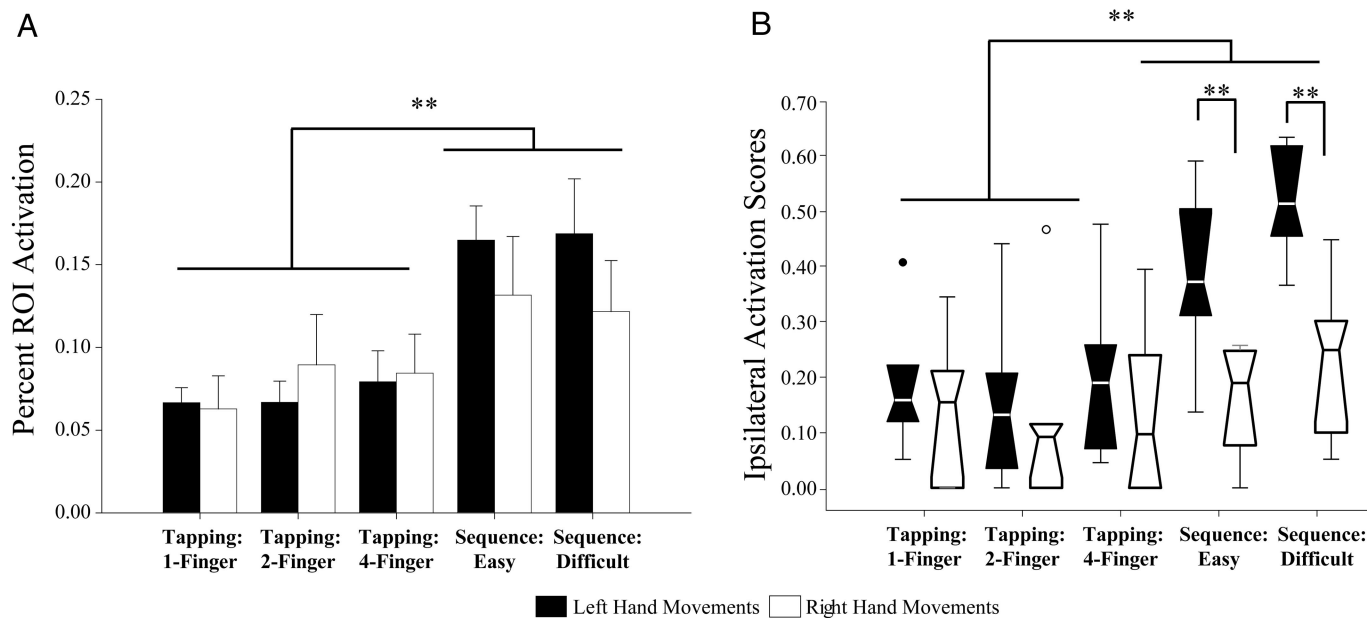


FIG. 7. A: percentage of suprathreshold voxels in both the left and right precentral gyrus ROIs for all movement conditions in *experiment 2*. The 2 sequence movements resulted in more overall activation and somewhat more activation during left-hand movements than the 3 tapping conditions. B: the Tukey boxplots show the distributions of ipsilateral activation coefficients distributed across all movement conditions. Consistent with *experiment 1*, left-hand movements resulted in greater ipsilateral responses than right-hand movements. The magnitude of these responses only increased in the 2 sequence conditions, indicating that the ipsilateral motor cortex is not simply responding to the number of fingers required in the movement.

cutting a sequence of responses (*experiments 1 and 2*) or adopting relatively novel hand configurations (*experiment 1*).

DISCUSSION

Movement complexity and the recruitment of the ipsilateral motor cortex

The current set of experiments was designed to investigate the factors influencing ipsilateral activation in the motor cortex during unimanual hand movements. Previous neuroimaging studies have consistently observed more ipsilateral activation during left- than during right-hand movements in the sensorimotor cortex of right-handed participants. Many of these studies have used a sequential finger opposition movement (Kawashima et al. 1993; Kim et al. 1993). This raises the question of how much of this effect is specific to the sequential demands of the task. Some theorists have sought a common mechanistic account for a left hemisphere specialization in language and action, arguing that both require an ability to represent sequential relationships (e.g., Corballis 1991). We developed the chord task in *experiment 1* to assess whether the involvement of the left hemisphere during left-hand movements was specific to sequences or whether it would be observed in a nonsequential complex movement task as well.

The results of *experiment 1* indicate that recruitment of the left hemisphere during ipsilateral movements does not require that the task involve the production of sequential movements. We found a similar degree of ipsilateral involvement during left-hand movements for both sequences and chords. While we did observe some ipsilateral activation when participants tapped with their left index finger, the extent of this activity was greatly reduced in comparison to the two more complex conditions.

The current results are consistent with the hypothesized specialization of the left hemisphere in the representation of

complex actions. For example, the problems patients with apraxia have in making coordinated and purposeful movements is most commonly observed after left hemisphere lesions (Heilman 2000; Keretsz and Hooper 1982; Liepmann 1907). Functional imaging experiments have also found increased activation in left parietal and premotor regions during complex, sequential movements but not simple tapping movements, regardless of which hand was used to perform the task (Haaland et al. 2004). Thus the left hemisphere may be preferentially involved in the coordination of complex movements. One possibility is that long-term representations of these actions are associated with the left hemisphere (e.g., Heilman 2000). Alternatively, the left hemisphere may be specialized for the rapid selection of learned sensorimotor associations, and this operation is especially taxed during complex actions (Schluter et al. 1998, 2001). By these hypotheses, the left hemisphere specialization is not necessarily related to the execution of complex movements but rather higher level operations associated with action retrieval, preparation, and/or selection.

We designed the chord task to involve relatively complex and novel gestures, while not requiring sequential movements. It could be argued, however, that our chord task did include a sequential component, and this may underlie the similar asymmetry results for the two complex tasks. For the chord task, participants were required to alternate between producing the three-finger chords and a simple thumb response. This alternation might, in a sense, constitute a sequence. We included the thumb response to increase the demands of this task. If participants were simply required to produce the same three-finger chord repeatedly, they could adopt a fixed posture and produce the movements at the wrist. By including the thumb response, participants reconfigured the fingers prior to each chord response. Thus although this task included a sequential

component, its complexity arose from the configural aspects of the task rather than from the minimal sequencing demands.

Another concern is that our tasks did not only differ in the degree of complexity but that other factors might have contributed to the differences in ipsilateral activation found in *experiment 1*. For example, both the chord and sequence movements required the coordination of multiple fingers on each trial, whereas tapping movements involved a single finger on each trial. We tested this effect in *experiment 2*, and the results confirm that ipsilateral response is not related to the number of fingers required for the action. The degree and asymmetry of motor cortex activation were similar for the tapping tasks regardless of whether one, two, or four fingers were used. Most importantly, the extent of the ipsilateral involvement during left-hand sequence movements in *experiment 2* was much greater than during the simple four-finger tapping task.

While ruling out an alternative explanation for the task effects in *experiment 1*, we are still limited in our ability to specify the exact conditions that lead to activation of ipsilateral motor cortex. Rather, the current study helps specify the appropriate boundary conditions. At one end, ipsilateral activation is not a simple function of the number of digits that must be coordinated. At the other end, ipsilateral activation is not limited to sequential actions. As a rough metric of complexity, we have used here the number of movements that can be made with a certain accuracy within a given time window, akin to the index-of-difficulty introduced by Fitts (1954). However, future studies may suggest a better metric, perhaps based on the degree of asynergistic activity required by the task or the number of elements needed to describe the movement pattern. Although not significant, we found a trend that a six-element sequence led to higher activation than a four-element sequence, lending some credibility to this idea.

Handedness as a factor

Handedness, defined as the preference to use one hand for everyday behaviors (Oldfield 1971), might be another factor that influences asymmetries in ipsilateral activation. If asymmetries of motor cortex activity were related to handedness, then the pattern for left-handed people should be the mirror reverse of that found in right-handed people. In contrast, if the asymmetries in ipsilateral activation are related to hemispheric specialization, then similar results should be found for left- and right-handed participants, similar to what has been found for patient studies on skill learning (Heilman 2000; Lausberg et al. 1999). A weaker form of the hemispheric specialization hypothesis is that left-handed persons might show a decreased magnitude of this leftward bias of ipsilateral activation, similar to what has been observed in imaging studies of language function (Pujol et al. 1999).

The results from *experiment 1* favor the latter hypothesis. All of the left-handed participants showed a strong left-hand preference on the Edinburgh inventory. Nonetheless, their activation profiles were mixed. On the sequence and chord tasks, half of the left-handed persons showed more ipsilateral activation when using their left hand, similar to what was observed in the right-handed people. Only one left-handed participant showed a reversed pattern with greater ipsilateral activation when using the right hand. The extent of ipsilateral

activation was roughly symmetric in the remaining left-handed people. Thus whereas the results were consistent for right-handed persons, the left-handed people present a mixed picture.

Previous findings regarding ipsilateral activation in left-handed people have been inconclusive. Kim et al. (1993) reported that left-handed persons exhibited stronger ipsilateral activity in the left hemisphere compared with the right, indicating a special role of this hemisphere in motor control. In contrast, Kawashima et al. (1993, 1997) observed greater ipsilateral activation when participants used their nondominant hand, regardless of handedness. Finally, to muddy the story even further, Singh et al. (1998) reported that left-handed people had equivalent amounts of ipsilateral activation regardless of which hand they used.

These discrepancies may be accounted for by two factors. First, left-handed people may be a highly heterogeneous group, at least in terms of neurological organization. Being "left-handed" is often defined as the preference for using the left hand in daily activities, such as writing or drawing (Oldfield 1971). This left-hand preference, however, does not necessarily imply a complete reversal of all functional brain asymmetries observed in right-handed participants. For example, most left-handed participants show a left-hemisphere specialization for language functions (e.g., Pujol et al. 1999). Our findings suggest that, although all left-handed people showed a strong preference for the left hand, only one of the eight subjects showed a reversal of the asymmetric activation during both complex movements.

Second, the discrepant results may be related to the different behavioral tasks that were used. Kim et al. (1993) used a sequencing task in which the participants touched each finger to the thumb in a repeating pattern. Kawashima et al. (1997) used a simple finger tapping task. Our results show that the magnitude of the ipsilateral activity (relative to overall activity) and the asymmetry of this activity between left and right hemispheres is much stronger in complex than in simple tasks. Taken together with the findings of Kim et al. (1993) and Kawashima et al. (1997) our results indicate that the pattern of ipsilateral motor cortex activity in left-handed persons also depends on characteristics of the movement.

Spatial characteristics and function of ipsilateral activity

We observed that the spatial locus of peak activation for ipsilateral movements was more anterior, lateral, and ventral than the locus for contralateral movements. This shift is consistent with a previous fMRI report (Cramer et al. 1999) and results from the TMS literature. For example, the optimal location for eliciting ipsilateral motor-evoked potentials (iMEPs) in distal arm muscles is located laterally and slightly forward of the location optimal for eliciting contralateral MEPs (Ziemann et al. 1999). These findings suggest that the ipsilateral activity reflects a network of neurons within precentral gyrus that are distinct from those associated with the control of contralateral movement.

As noted in the INTRODUCTION, cytoarchitectonic studies define two distinct regions in the precentral gyrus (for review, see Geyer et al. 2000). Brodmann's area 4, the primary motor cortex, occupies the posterior portion of the gyrus and extends into the central sulcus. The anterior

portion of the precentral gyrus has been identified as a subregion of Brodmann's area 6 (BA 6a) and is considered to be a subdivision of premotor cortex. The precise boundary between these two regions cannot be identified using the macroscopic landmarks available with MRI. Therefore it is difficult to conclusively determine whether the center of activation during ipsilateral hand movements was in primary motor or premotor cortex. However, the spatial shift in activation between the contra- and ipsilateral hand movements is more consistent with a premotor locus. The magnitude of the shift spanned almost the entire width of the precentral gyrus, resulting in activation centers that approached the precentral sulcus. Note that, with respect to human motor cortex, the distinction between area 4 and 6a is based solely on the density of descending pyramidal cells; the functional correlates of this anatomical difference has yet to be determined.

What might be the functional role of the observed ipsilateral response? The execution of movements requires the generation of spatiotemporal patterns of activity in the contralateral motor cortex. We hypothesize that when this pattern is very complex and when the contralateral hemisphere is not well trained in the production of this task, the ipsilateral motor cortex can help shape the appropriate pattern through both excitatory and inhibitory connections. This hypothesis is consistent with our finding that the degree of ipsilateral activation increases with task complexity and also that it is more pronounced during left- than during right-hand movements. Furthermore, the performance differences between the two hands were correlated with the asymmetry in ipsilateral activation of the two hemispheres, such that ipsilateral activation was strongest when participants used their less proficient hand to produce the actions. For participants who showed no clear performance differences between hands, the degree of ipsilateral activity was symmetric. The proposed functional role of ipsilateral activity during execution rather than during planning of the movement is also supported by findings from a TMS study which reported that stimulation over the left motor cortex impaired sequential movements of the ipsilateral hand (Chen et al. 1997).

There are two possible pathways through which the motor cortex could modify the command to the ipsilateral hand. First, the influence could be direct via descending ipsilateral projections to the spinal cord. In accordance with this hypothesis, a previous experiment by Ziemann and colleagues (1999) found that TMS of the motor cortex elicited iMEPs in a patient with complete agenesis of the corpus callosum. Furthermore, the spatial locus of peak activation for ipsilateral movements found in our study corresponds approximately to the region where TMS stimulation maximally elicits iMEPs.

Alternatively, the influence could be mediated by callosal projections from the ipsilateral motor cortex to the contralateral motor cortex. While some of these projections are excitatory, some synapse on interneurons that in turn inhibit the neurons that descend to the distal muscles (Chen et al. 2003; Daskalakis et al. 2002). Interestingly, it has been found that callosally mediated projections to the inhibitory interneurons also show an asymmetric efficiency. Specifically, the left motor cortex has a greater inhibitory effect on the right motor cortex than vice versa, regardless of an individual's handedness (Netz et al. 1995). The stronger

inhibitory influence through callosal fibers could be one mechanism through which the left hemisphere helps shape complex actions performed with the left hand. Findings from a recent study by Kobayashi and colleagues (2003), lends credence to this hypothesis by showing that the presence of left motor cortex BOLD responses during ipsilateral hand movements corresponds to modified patterns of interhemispheric inhibition assessed using TMS.

Of course, the descending ipsilateral pathways and inter-hemispheric communication hypotheses are not mutually exclusive. It is possible that the observed ipsilateral activity in the present study reflected neural activity related to ipsilateral descending signals and callosally mediated interactions with the contralateral hemisphere. Disassociating these two circuits is a question for future studies.

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