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ORIGINAL ARTICLE

Mirror Motor Activity During Right-Hand Contractions and Its Relation to White Matter in the Posterior Midbody of the Corpus Callosum

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Abstract

Cortical activity during simple unimanual actions is typically lateralized to contralateral sensorimotor areas, while a more bilateral pattern is observed with an increase in task demands. In parallel, increasing task demands are associated with subtle mirror muscle activity in the resting hand, implying a relative loss in motor selectivity. The corpus callosum (CC) is crucially involved in unimanual tasks by mediating both facilitatory and inhibitory interactions between bilateral motor cortical systems, but its association with mirror motor activity is yet unknown. Here, we used diffusion-weighted imaging and bilateral electromyographic (EMG) measurements during a unimanual task to investigate potential relationships between white matter microstructure of the CC and mirror EMG activity. Participants performed an unimanual pinch force task with both hands alternatively. Four parametrically increasing force levels were exerted while EMG activity was recorded bilaterally from first dorsal interosseus muscles. Consistent with previous findings, mirror EMG activity increased as a function of force. Additionally, there was a significant relationship between the slope of increasing mirror EMG during right-hand contractions and fractional anisotropy in transcallosal fibers connecting both M1. No significant relationships were found for fibers connecting dorsal premotor cortices or supplementary motor area, indicating the local specificity of the observed brain–physiology relationship.

Key words: dorsal premotor cortex, mirror EMG activity, motor overflow, primary motor cortex, supplementary motor area

Introduction

Humans and other primates share the capability to move one hand relatively independent from the other, allowing for a wide repertoire of uni- and bimanual movements. However, some movement patterns are more stable than others: There is a natural tendency to perform mirror-symmetrical movements (simultaneous contractions of homologous muscles) when compared with alternating movements (simultaneous contractions of nonhomologous muscles; Kelso et al. 1979; Swinnen and Wenderoth 2004).

During strictly unimanual contractions, interhemispheric interactions involving primary motor (M1) and premotor areas are required to restrict the motor output to the intended hand (Giovannelli et al. 2006; Hubers et al. 2008; Fling and Seidler 2012a, 2012b). Neurological disorders, such as stroke or Parkinson's disease, may result in a breakdown of this network and lead to pronounced mirror movements (Cincotta and Ziemann 2008). However, the suppression of mirror movements is often incomplete even in healthy individuals—resulting in subtle mirror

motor activity in the "resting limb." This phenomenon is ubiquitous but highly variable across subjects and can be regarded as a remnant of the basic mirror-symmetrical movement mode. Furthermore, mirror electromyographic (EMG) activity increases as a function of the functional demand of the unimanual task, such as increasing levels of force (Sehm et al. 2010). Studying the neural correlates of mirror EMG activity provides a window into the fundamental principles of uni- and bimanual motor control. Concurrent functional MRI and EMG measurements have been used to identify a bilateral network involving primary motor cortex (M1) and the supplementary motor area (SMA) that is associated with mirror EMG activity (Sehm et al. 2010). Other studies showed that downregulation of neural processing in dorsal premotor cortex (PMd) by means of noninvasive brain stimulation using transcranial magnetic stimulation (TMS) results in increased mirror EMG activity (Giovannelli et al. 2006). The corpus callosum (CC) is the principal structure that propagates neural crosstalk between both hemispheres. The fine-tuned modulation of inhibitory and facilitatory mechanisms required for uni- and bimanual movements is provided by this structure (Swinnen 2002). However, it still remains elusive whether this structure is also related to mirroring.

Here, we used diffusion-weighted imaging (DWI) and bilateral EMG measurements during a unimanual task to investigate potential relationships between white matter microstructure of the CC and mirror EMG activity. We hypothesized that interindividual variations in fiber connections between M1 representing the first dorsal interosseus muscle (FDI) would be linked with mirror EMG activity. To specify the unique contribution of M1–M1 connections over the potential effects of interconnected regions, we also included assessments of interhemispheric PMd and SMA connections in the analysis.

Methods

Subjects

Twenty healthy volunteers (10 female; mean age 27.9 ± 2.9 SD) participated in this study. The ethics committee of the University of Leipzig approved this study, and all subjects gave written informed consent to participate in the experiment according to the Declaration of Helsinki. Subjects that had contraindications for MRI measurements were excluded from participation. According to the Oldfield questionnaire for the assessment of handedness (Oldfield 1971), all subjects were right-handed (laterality quotient of 94.25 ± 8.2; mean ± SD).

Motor Task

For the motor task, subjects were seated comfortably in a chair with both arms flexed at the elbow. They held a custom-made pressure sensor between the thumb and index finger of one hand (Fig. 1*A*), whereas the other hand rested on a table. Unimanual isometric pinch forces were exerted with first one hand, then the other, consecutively. Order was counterbalanced across subjects to eliminate order effects. Subjects were initially asked to exert their maximum pinch force 3 times for each hand. These measurements were averaged to calculate their force at maximum voluntary contraction (MVC) for each hand. Subjects were then asked to perform an individually adjusted pinch force task at 4 different levels (10%, 20%, 30%, and 70% of the MVC). Subjects were instructed to apply isometric pinch force to move a cursor to a stationary target box presented on a computer monitor as fast and as accurately as possible. The target box location, and the force required to reach it with the cursor, was adjusted to each individual's maximal pinch force (i.e., greater distances required higher levels of force generation). Subjects were instructed to maintain the cursor in the target box for 2 s with continuous isometric pinch force (Fig. 1*B*). The force applied to the sensor was digitally sampled at 100 Hz and displayed on the computer screen at 60 Hz. After each trial, subjects rested for 4 s, before the target signal again appeared on the screen. Twenty trials were performed for each force level and each hand, resulting in 80 pinch movements per hand. The 4 different force levels were pseudorandomized within each individual, in order to ensure that factors, such as muscle fatigue, had no systematic effect on the amount of force-dependent mirror EMG activity.

EMG Recordings and Analysis

EMG activity was recorded bilaterally from the FDI on both the moving and resting hand (Fig. 1*C*) with surface electrodes in a bipolar montage. This set-up allowed us to assess EMG activity over the primary moving muscle (FDI) as well as subliminal mirror EMG activity over the homologous FDI of the resting limb [Fig. 1*D*; see also Sehm et al. (2010)].

EMG data were analyzed offline using Spike2 (Cambridge Electronic Design, Cambridge, UK). EMG signals were rectified, and the mean EMG activity was obtained, trial-by-trial, from both recorded muscles. The onset of each EMG burst of the FDI of the moving hand was defined as the time point when the mean EMG activity exceeded the baseline activity (BL) by 3 SD (BL + 3 SD). The offset of each EMG burst was defined as the time point when the EMG signal fell below this value. EMG recordings from either FDI were time-locked to on- and offset of the voluntary burst in the voluntary moving FDI. Next, EMG data were expressed as the percentage change of baseline EMG activity. The 20 trials in each condition were averaged prior to further analyses.

Repeated-measures analyses of variance ($ANOVA_{RM}$) were used to determine the effect of FORCE (10%, 20%, 30%, and 70%) and SIDE (left hand and right hand) on each muscle EMG. In case of a violation of the sphericity assumption, Greenhouse–Geisser correction was performed. Post hoc testing was performed using a Bonferroni-corrected significance threshold. *P*-values <0.05 were regarded as significant.

In addition, the same analysis [$ANOVA_{RM}$ with the factors FORCE (10%, 20%, 30%, and 70%) and SIDE (left hand and right hand)] was performed to identify potential influences of these factors on the EMG burst duration of the FDI of the moving hand.

To assess potential time-dependent influences on mirror EMG activity during the course of the experiment, we performed an additional $ANOVA_{RM}$ with the factors FORCE (10%, 20%, 30%, and 70%), SIDE (left hand and right hand), and TIME (trial 1, . . . , trial 20). We also asked whether mirror EMG activity might be related to the speed of each participant's task performance. Here, we performed correlation analyses between the time required for each individual to finish the motor task with one hand and their respective mirror EMG activity.

On an individual level, we computed the slope of mirror EMG activity across force levels as a compound measure—referred to as mirror recruitment. This served as the primary outcome measure capturing the amount of recruitment of motor activity in the "resting" limb across the different force levels. Mirror recruitment was then correlated with fractional anisotropy (FA, see below) of the callosal fibers connecting primary and secondary motor areas.

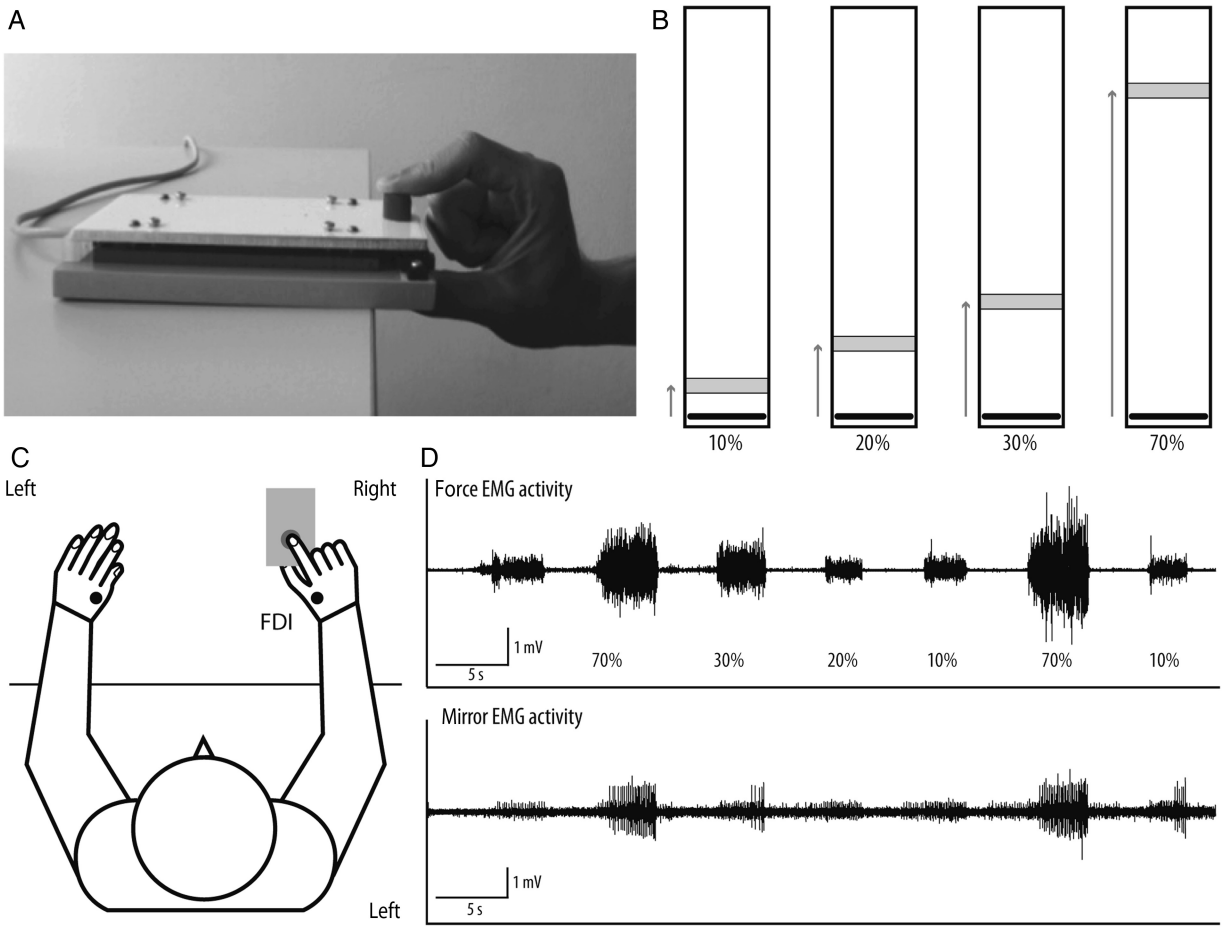

Figure 1. Experimental set-up. (*A*) Participants were sitting in front of a computer screen and controlled on-screen cursor movements by exerting pinches with the thumb and index finger on a force transducer. (*B*) Diagram showing the visual display presented to all subjects during testing. The black horizontal line shows the cursor that participants were instructed to move by performing right and left isometric pinch forces over the force transducer. The gray box located above the cursor illustrates the target to which subjects had to move the cursor, maintaining it in position for 2 s. The distance between the cursor and the target related to the magnitude of force required to accomplish each task, normalized to the maximal pinch force determined in each participant. (*C*) EMG was recorded from the left and right FDI during unimanual contractions. (*D*) Traces showing EMG recordings in the right (primary mover) and left FDI (homologous muscle of the resting limb) of a representative subject. Note the presence of mirror EMG activity in the left FDI during 10%, 20%, 30%, and 70% of maximal right pinch force.

Scanning Protocol

Subjects were scanned on a 3-T Magnetom Tim Trio scanner (Siemens) using a 32-channel head coil. We acquired whole-brain DWI with a double spin echo sequence using the following parameters: 60 directions; *b*-value = 1000 s/mm^2; 88 slices; voxel size, 1.7 × 1.7 × 1.7 mm, no gap; repetition time = 12.9 s; echo time = 100 ms; field of view = 220 × 220 mm; GRAPPA acceleration factor = 2. Seven volumes without diffusion weighting (b = 0 s/mm^2) were acquired, one at the beginning of the sequence and after each block of 10 diffusion-weighted images. The acquisition time for the scan was approximately 15 min.

MRI Data Processing and Analysis

DWI were corrected for motion and eddy current distortions before calculating voxel-wise maps of FA with the FMRIB Software Library (FSL v 5.07; Smith et al. 2004). FA images were then nonlinearly coregistered to the FMRIB_FA 1 mm standard with the registration step available in the tract-based spatial statistics pipeline in FSL. We next created 4 bilateral pairs of 5 mm radius spherical regions of interest (ROIs) to use as seed/target masks for M1 (±33, −21, 52), PMd (±30, 4, 52), SMA (±10, −7, 58), and primary somatosensory cortex (S1) (±36, −33, 52) (all coordinates are reported in MNI space and symmetric across hemispheres). Individual seed ROIs were created and confirmed in a three-step process. First, ROI coordinates for the sensorimotor seed regions were taken from a recent meta-analysis (Mayka et al. 2006) and adjusted to ensure that they were centered on the white matter in the group mean FA map. Second, each ROI was inversely transformed into individual space and restricted to the white matter by thresholding at FA >0.2. Third, to be as precise as possible, ROIs were overlaid on individual FA maps to confirm their location in individual space. This combination of literature-derived ROI selection, nonlinear registration for transformations, and manual confirmation on individual anatomy ensured that the seed regions were as reproducible and specific as possible. An additional projection of the M1 ROIs onto T_1-weighted native space was also performed for further confirmation (see Supplementary Fig. 2). These steps produced the final native-space target/seed masks that were used in the tractography analyses described below. A waypoint mask in the CC and 2 exclusion masks were also created for the individual-space tractography. The corpus callosal waypoint mask was initially hand drawn

on the group mean FA image to include all slices between $x = -4$ and 4. The group mask was then transformed into individual space, and thresholded at FA >0.2 for each individual. In addition, one exclusion mask was placed in the midline superior to the CC from $x = -1$ to $x = 1$ to ensure no spurious streamlines between the gray matter of the hemispheres, and another was placed in the axial plane inferior to the CC from $z = -14$ to $z = -12$ to further limit streamlines to those passing directly through the CC (see Supplementary Fig. 1). Both exclusion masks were also transformed into individual space prior to tractography.

Additional preprocessing of diffusion images and probabilistic tractography between homologous ROIs was performed with MRtrix (v0.2.11; Tournier et al. 2007). The fiber orientation distribution function was derived with constrained spherical deconvolution (CSD) using a maximum spherical harmonics order of 8, and the single-fiber response function necessary for CSD was calculated from all voxels where FA >0.7. Probabilistic tractography was performed twice for each set of homologous seeds, with 200 streamlines each. Standard MRtrix tracking parameters were used (step-size = 0.2 mm, FOD amplitude cutoff and initial cutoff = 0.1, minimum/maximum length = 10/200 mm). The corpus callosal waypoint mask and 2 exclusion masks were used to restrict the results to streamlines directly connecting homologous ROIs. Tractography with this method produced 2 sets of streamlines connecting the homologous ROIs through the CC: one from left → right and the other from right → left.

The 2 sets of streamlines were then combined to pinpoint the exact locations of the interhemispheric connections between homologous ROIs. The left → right and right → left streamlines were converted into voxel-wise visitation maps, summed, thresholded to remove voxels with visitations counts below 5% of robust maximum, and binarized. These masks were then multiplied by the individual callosal FA masks to create the final callosal masks for M1, PMd, SMA, and S1. In a final step, individual FA maps were minimally smoothed (Gaussian kernel, sigma = 2 mm) and mean FA from each callosal mask was extracted for the correlational analyses described below. In a separate step, the binarized individual masks were transformed into standard space and summed to create population visitation maps displaying each set of connections. Finally, correlation between mirror recruitment and extracted FA values (M1, PMd, SMA, and S1) was performed using SPSS for windows version 22. Additionally, partial correlation analysis was performed to correlate the specific contributions of one tract while controlling for potential influences of the others.

Results

EMG Activity of the Moving and "Resting" Hand

Figure 1*D* illustrates representative intercepts of bilateral EMG recordings of the FDI during voluntary unimanual pinch forces at 4 different force levels (10%, 20%, 30%, and 70% of MVC). Group mean data are shown in Fig. 2*A–D*. In line with previous findings, increasing force levels lead to an increase in EMG activity in the left and the right FDI (Fig. 2*A*,*D*). This effect was supported by a significant main effect of FORCE ($F_{3,57} = 57.67$, $P < .001$). There were no differences between the left and right side (SIDE: $F_{1,19} = 1.16$, $P = 0.29$), nor was there an interaction FORCE × SIDE ($F_{3,57} = 1.59$, $P = 0.20$; Greenhouse–Geisser-corrected). Post hoc testing revealed significant differences between all force levels both during left- and right-handed contractions ($P < 0.0083$; Bonferroni-corrected for all 6 comparisons).

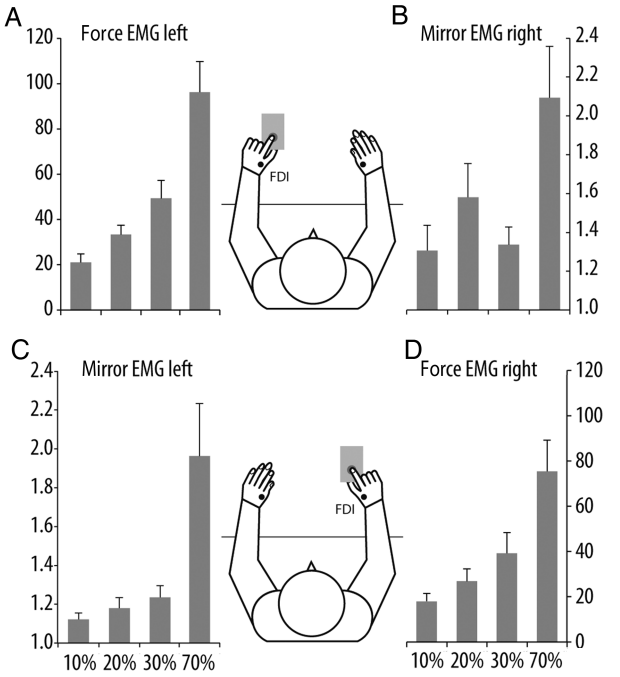

Figure 2. Group EMG data. In all graphs, the abscissa shows the conditions tested (10%, 20%, 30%, and 70%) and the ordinate shows the mean rectified EMG activity (expressed as percent changes of baseline) during voluntary contractions (*A*: left FDI; *D*: right FDI) and during contractions of the contralateral limb, corresponding to mirror EMG activity (*B*: right FDI; *C*: left FDI).

The EMG burst duration of the voluntary moving FDI differed between force levels [mean (±SD)]: left FDI at 10% = 3.00 s (±0.36); 20% = 3.29 s (±0.4); 30% = 3.45 s (±0.40); 70% = 4.27 s (±1.010); right FDI 10% = 3.04 s (±0.34); 20% = 3.2 s (±0.32); 30% = 3.43 s (±0.43); 70% = 4.08 s (±1.07). This was supported by an ANOVA for repeated measurements with factors FORCE (10%, 20%, 30%, and 70% of MVC) and SIDE (left and right) on "burst duration"; FORCE: $F_{3;57} = 21.93$; $P < 0.01$; SIDE: $F_{1;19} = 0.52$; $P = 0.48$. No differences in burst duration were found between hands.

Importantly, EMG activity in the homologous muscle of the "resting" hand (i.e. mirror EMG) was observed during voluntary contractions of the opposite hand (Figs 1*D* and 2*B*,*C*). FORCE had a significant influence on the amount of mirror EMG activity (FORCE: $F_{3,57} = 22.98$, $P < 0.001$, Greenhouse–Geisser-corrected). No significant effect was found for the factor SIDE ($F_{1,19} = 1.68$, $P = 0.27$) or the interaction FORCE × SIDE ($F_{3,57} = 0.8$, $P = 0.50$). Post hoc testing revealed differences in mirror EMG activity between 30% and 70% of MVC both in left FDI ($P = 0.009$; nonsignificant trend) and in right FDI ($P = 0.0005$). The Bonferroni-corrected threshold for all 6 comparisons (left FDI: 10% vs. 20%; 20% vs. 30%, and 30% vs. 70% of MVC; right FDI: 10% vs. 20%; 20% vs. 30%, and 30% vs. 70% of MVC) was set at $P < 0.0083$.

The mean slope of increasing mirror EMG across force levels was 0.015 (±0.020; mean ± SD) for the left FDI during contractions of the right-hand and 0.013 (±0.011) for the right FDI during left-hand contractions.

An additional analysis was performed to assess potential time-dependent influences on mirror EMG activity over the course of the experiment. This analysis confirmed the previously described effects of force on mirror EMG activity, but did not show any time-dependent changes in mirror EMG activity (FORCE: $F_{3,48} = 16.9$, $P < .001$; SIDE: $F_{1,16} = 0.08$, $P = 0.78$; TIME: $F_{3.8,60.92} = 4.00$, $P = 0.29$; FORCE × SIDE: $F_{1.06,17.01} = 4.05$, $P = 0.38$; SIDE × TIME:

$F_{4.30,68.81} = 0.19$, $P = 1.0$; FORCE × TIME: $F_{6.30,100.85} = 0.91$, $P = 0.65$; FORCE × SIDE × TIME: $F_{6.31,100.95} = 1.20$, $P = 0.31$).

The time to complete the experiment showed only slight intersubject variability [right hand 6.9 min ± 0.03; left hand 6.9 min ± 0.03 (mean ± SD)]. No correlation was found between the time to complete and mirror recruitment (right FDI $r = -0.12$; $P = 0.63$; left FDI $r = -0.23$; $P = 0.36$).

Fiber Tractography

Interhemispheric fiber tracts were found for all brain areas tested: M1, PMd, SMA, and S1 (Fig. 3). In agreement with previous reports (Fling et al. 2013), the fiber tracts were found in an anterior–posterior shift: PMd and SMA fibers anterior from M1 and S1. Fiber tracts of M1 and PMd were largely overlapping, but also showed a rostro-caudal arrangement, with the center of the PMd fibers being localized caudally from the SMA fibers (Fig. 3, close-up).

Relationships Between FA of the CC and Mirror EMG Activity

A correlation analysis controlling for sex and age was used to investigate the relationships between mirror recruitment of the left FDI and FA of the CC in 3 different interhemispheric fiber tracts: M1, SMA, and PMd fibers. There was a significant relationship between mirror EMG and FA in M1 ($r = 0.69$; $P = 0.001$) and SMA ($r = 0.53$; $P = 0.017$) interhemispheric connections. No significant correlation was found for PMd ($r = 0.41$; $P = 0.075$; Fig. 4A). As expected, the S1 control analysis (correlation of interhemispheric S1 fibers and mirror recruitment of the left FDI) was also not statistically significant ($r = 0.19$; $P = 0.448$). Additionally, we chose another control in a region of the CC that connects bilateral primary visual cortices. We chose this confirmative control region, because it shares dense interhemispheric connections, but is remote from sensorimotor fibers. No significant relationship was found ($r = -0.11$; $P = 0.66$).

Since there were significant correlations between FA and mirror EMG in M1 and SMA interhemispheric connections (Fig. 4A), we performed additional partial correlation analyses to correlate the specific contributions of one tract while controlling for the effects of the others. Interestingly, only FA from M1 was significantly correlated with mirror EMG ($r = 0.69$; $P = 0.003$)—providing evidence that the observed mirror EMG activity is primarily affected by M1–M1 connectivity. There was no correlation for SMA ($r = 0.37$; $P = 1.00$) or PMd ($r = -0.23$; $P = 0.385$) (Fig. 4B,C).

Furthermore, no significant relationship was found for mirror recruitment in the right FDI for M1 ($r = -0.07$; $P = 0.79$), PMd ($r = -0.01$; $P = 0.97$), SMA ($r = 0.05$; $P = 0.86$), and S1 ($r = 0.22$; $P = 0.37$).

The tractography of transcallosal PMd and SMA fibers showed a certain amount of overlap of their representations in the CC

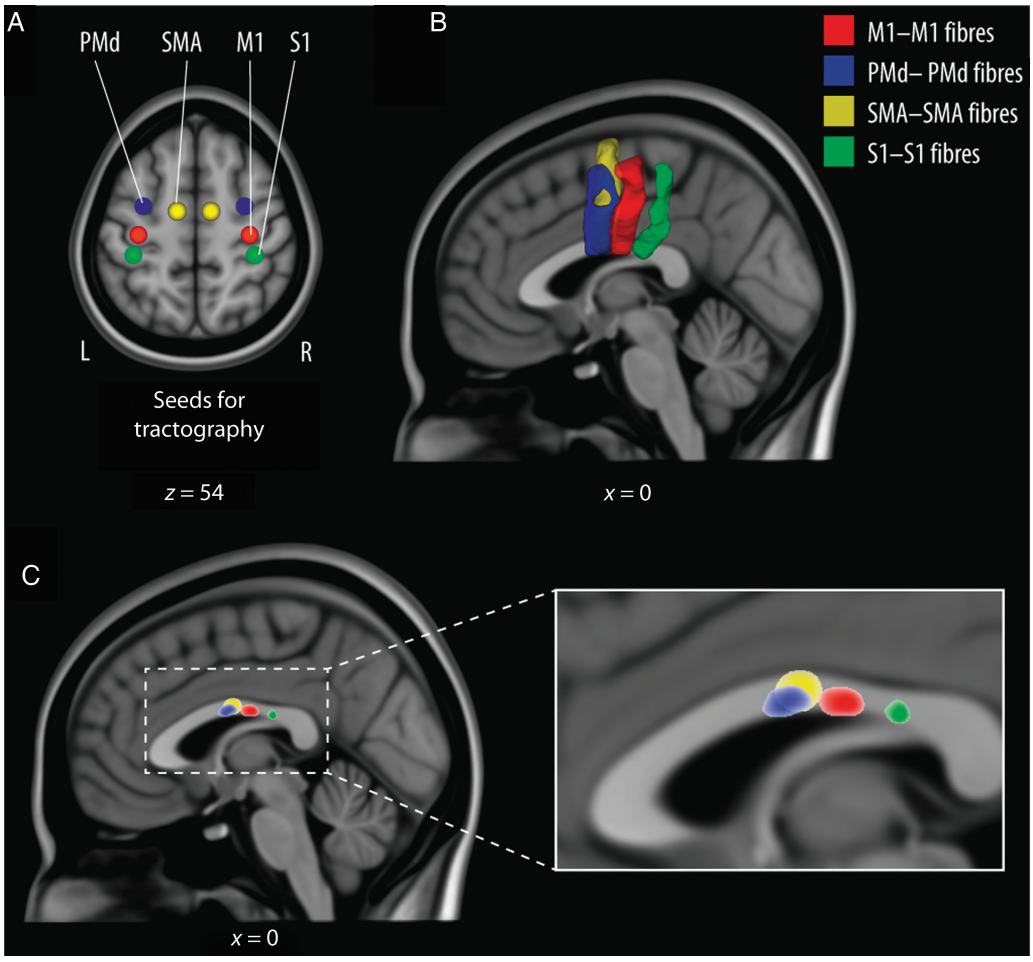

Figure 3. Probabilistic tractography of transcallosal fibers using DWI. (*A*) Seed regions for interhemispheric tractography in bilateral M1, S1, SMA, and PMd. (*B* and *C*) Interhemispheric fiber tracts were found for all brain areas tested. Note the craniocaudal somatotopic and partially overlapping topography of the callosal fibers connecting bilateral M1, SMA, and PMd.

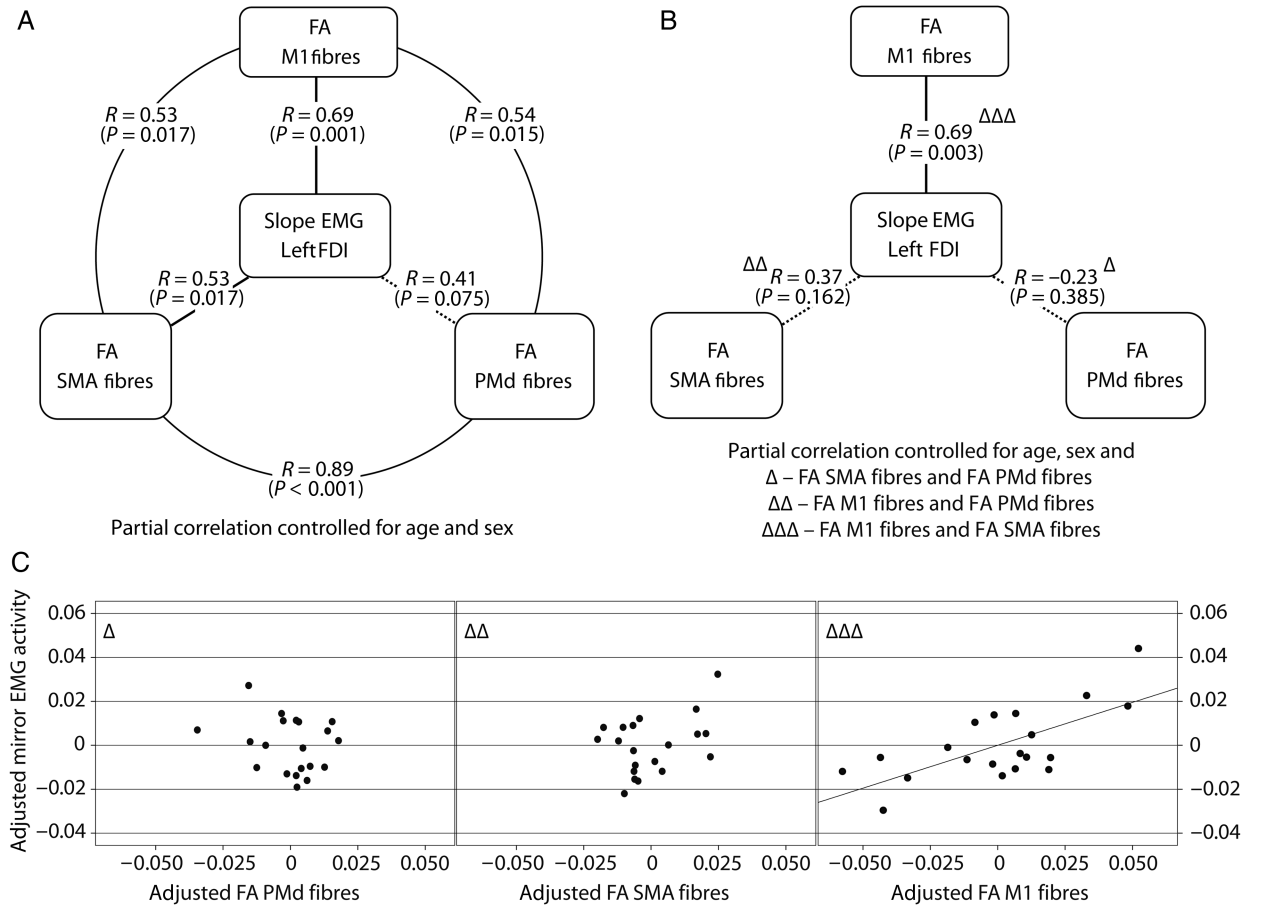

Figure 4. Relationship between the microstructure of interhemispheric fiber tracts and the tendency for mirroring. (*A*) Results of a partial correlation analysis controlling for sex and age showing significant relationships between the mirror recruitment of left FDI and M1 and SMA fibers. However, this result might be influenced by significant correlations between FA values in the 3 different fiber tracts (external circle). (*B*) Results of a partial correlation analysis controlling for sex, age, and FA of the other 2 fiber tracts, respectively. This analysis revealed a specific relationship between mirror recruitment of left FDI and M1 fibers, but not for SMA or PMd fibers. (*C*) Scatterplots of the brain–physiology relationships as established by the partial correlation analysis in (*B*). FA values are adjusted to the controlled variables sex, age, and the FA of the tracts that were not correlated in the respective analysis.

(Fig. 3). Hence, an additional partial correlation analysis was performed between mirror recruitment and FA of the CC using only FA from voxels where there was no overlap. This analysis confirmed the previous results and showed only a significant correlation for M1–M1 transcallosal FA: mirror recruitment of left FDI and M1 FA ($r = 0.77$; $P = 0.001$; controlled for age, sex, PMd FA, and SMA FA); mirror recruitment of left FDI and PMd FA ($r = -0.17$; $P = 0.52$; controlled for age, sex, SMA FA, and M1 FA); mirror recruitment of left FDI and SMA FA ($r = 0.51$; $P = 0.04$; controlled for age, sex, PMd FA, and M1 FA).

Discussion

We investigated the association between mirror EMG activity during parametric increases in unimanual force generation of the opposite hand and white matter structure of the CC. Mirror EMG was observed during both right- and left-handed contractions and increased as a function of force. Probabilistic tractography revealed a craniocaudal somatotopic organization of transcallosal fibers connecting bilateral S1, M1, PMd, and SMA. Importantly, we found a significant association between mirror EMG activity during right-hand contractions and FA of fiber tracts connecting M1 and SMA. No such relationship could be observed for fiber tracts connecting bilateral PMd or S1. Since FA of fiber tracts of M1, PMd, and SMA was mutually correlated, we performed a partial correlation analysis to show which fiber tracts directly contribute to EMG mirror activity. We found that FA of M1 fiber tracts is directly linked to mirror EMG activity during right-hand contractions, while SMA might only indirectly contribute to mirroring.

Mirroring Depends on the Functional Demand During Unimanual Movements

The finding that mirror EMG activity was observed during a range of low- and high-force contractions of the opposite hand underlines the ubiquitous presence of this phenomenon during unimanual actions. Consistent with previous studies, we demonstrate that mirror EMG increased as a function of the force applied by the opposite hand (Aranyi and Rosler 2002; Zijdewind et al. 2006; van Duinen et al. 2008; Sehm et al. 2010). These results highlight the intraindividual variability and task-dependency of this phenomenon. Moreover, this effect might not be specific to force but more generally related to the functional demand of the unimanual task: Previous studies showed that other modulators of task demand such as movement frequency (Uttner et al. 2007), level of fatigue (Post et al. 2008), or cognitive load (Bodwell

et al. 2003; Addamo et al. 2009) also were related to increases in mirroring. It has been suggested that mirror EMG activity can be regarded as remnant of an ontogenetic learning process to decouple both hands and perform independent hand movements (Uttner et al. 2007). We suggest that, in our study, an increase in force resulted in an unmasking of the more basic mirror-symmetrical movement mode.

Neural Correlates and Mechanisms of Mirror EMG Activity

While the neural underpinnings are still under debate (Carson 2005; Cincotta and Ziemann 2008), previous work provided evidence that a network of cortical and subcortical areas is involved in the generation of mirror EMG activity (Sehm et al. 2010). Two main hypotheses for a prominent role of M1 have been put forward: First, it has been suggested that uncrossed descending corticofugal fibers (~10–15% in healthy individuals) originating in M1 contralateral to a voluntary moving hand are causing this phenomenon. This view is mainly supported by clinical data of patients that exhibit overt mirror movements (for example, Cohen et al. 1991; Gallea et al. 2013). However, neural mechanisms underlying pathological mirror movements might be essentially different from those underlying "physiological" mirror EMG activity as investigated in the present study (Cincotta and Ziemann 2008).

A second hypothesis asserts that M1 ipsilateral to a moving hand generates mirror EMG activity via crossed descending corticofugal fibers. Accordingly, excitability in ipsilateral M1 increases in the presence of mirror EMG activity in healthy subjects (Zijdewind et al. 2006). Furthermore, fMRI studies in healthy individuals have shown an increase in activity in M1 ipsilateral to a contracting arm during strong unimanual force generation, when mirror EMG activity has been reported (Dettmers et al. 1995; van Duinen et al. 2008). These results raise the concept of disinhibitory interhemispheric influences from contralateral to ipsilateral M1. Here, we extend these findings and provide novel evidence that interindividual structural variations of transcallosal fibers connecting M1 are related to the tendency to exhibit mirror EMG activity. Interestingly, we only observed this relationship during dominant (right)-hand contractions.

Indeed, there is converging evidence that the amount of increase in contralateral activation (BOLD signal) during unimanual movements is correlated with that of inhibition from contra- to ipsilateral M1 (Sarfeld et al. 2012) or with that of decrease (negative BOLD) in ipsilateral M1 (McGregor et al. 2014). Both findings support the notion that ipsilateral motor cortical areas are actively suppressed by contralateral motor areas. One possible interpretation of this phenomenon is that these interactions prevent the occurrence of mirror movements, and that an overload of these mechanisms might result in mirror motor activity. The CC is the principal structure mediating inhibitory and/or facilitatory interhemispheric crosstalk, in order to enable independent hand movements. On this notion, the direction of the correlation in the present study is of special interest: Subjects with higher FA values showed more mirror EMG activity. While the exact biological underpinnings of FA still remain elusive, the degree of fiber myelination, axon size, and density likely play an important role (Beaulieu 2002; Le Bihan 2003). Given this, our results might suggest that transcallosal fibers mediating facilitation between M1 are driving the result. At first sight, this result seems contradictory with respect to previous studies using TMS to show that magnitudes of interhemispheric inhibition (IHI) between both M1 are inversely correlated with mirror EMG activity (Hubers et al. 2008; Fling and Seidler 2012a, 2012b). Similarly, it was demonstrated that the amount of interhemispheric facilitation is positively correlated with mirror EMG activity (Fling and Seidler 2012a, 2012b). However, different measures (TMS vs. DWI) might capture different aspects of similar underlying mechanisms. Only recently, Chiou et al. (2014) used DWI to determine FA of callosal fibers connecting both M1 for correlation with excitability changes in ipsilateral M1 during unimanual contractions. In line with our own results, they found a positive correlation between FA and increases in excitability in M1 ipsilateral, underlining the facilitatory properties of this fiber pathway. We extend these findings by showing that FA of this pathway might not only be related to facilitation of ipsilateral M1 but also to the emergence of mirror EMG activity during unimanual right-hand contractions. On this notion, previous studies have characterized facilitatory and inhibitory interactions between both M1. Accordingly, both animal models and human research demonstrated that evoked potentials can be recorded over one M1, following electrical or magnetic stimulation of the contralateral M1 (Hanajima et al. 2001; Chowdhury and Matsunami 2002). Experiments using paired-pulse TMS techniques applied over both M1 investigated interhemispheric interactions and demonstrated that, while inhibition was the most striking finding, also facilitation between both M1 occurs and represents a consistent finding across different studies (Ferbert et al. 1992; Hanajima et al. 2001; Baumer et al. 2006). Another study did not directly investigate facilitation between both M1, but the effects of increasing unimanual force on IHI showed that IHI from contralateral to ipsilateral M1 decreases with increasing wrist flexion force in healthy human subjects (Perez and Cohen 2008). The authors interpret their findings as a process involved in tuning the corticospinal motor output from the ipsilateral M1. Hence, at lower force levels, the overall net interhemispheric effect targeting M1 ipsilateral might be inhibitory, whereas at higher force levels there is an overall release of inhibition (Perez and Cohen 2008) that might contribute to mirror movements (Zijdewind et al. 2006). This interpretation is in line with the results of our own study. Indeed, early experiments in cats have shown that the cortical representation of the distal forelimb in M1 has a facilitatory transcallosal connection to the homologous motor cortex, but is surrounded by a large area of inhibition (Asanuma and Okuda 1962). Hence, it is tempting to speculate that such a facilitatory transcallosal pathway is driving the structure–function relationship between mirroring and transcallosal M1–M1 pathways in our own results.

Our findings revealed an asymmetry during dominant- compared with nondominant-hand movements both in the emergence of mirror motor activity across force levels, and, more importantly, in correlation with FA in the CC. In fact, the difference in mirror EMG activity between sides was very small with both the main effect of SIDE and the interaction FORCE × SIDE failing to reach significance. These results are in line with the general notion that mirroring is a phenomenon that may be observed both during contractions of the dominant and nondominant hand. The fact that, in our results, no clear lateralized pattern in the emergence of mirroring was observed is in line with differences in the results in previous studies. While some authors report stronger mirror activity during voluntary movement of the nondominant hand (Uttner et al. 2007), others found the reverse pattern (Cernacek 1961) or no differences between hands (Armatas and Summers 2001). Indeed, it was suggested previously that the asymmetry of mirror movements depends on the type of task and contributes to these conflicting results (for review Cincotta and Ziemann 2008). However, post

hoc testing revealed that there was a significant difference in the amount of mirror EMG activity between 70% and 30% of MVC in the right FDI, whereas this was observed on the left side as only a statistical trend. More importantly, there was also an asymmetry in terms of correlation: Only the left FDI mirror motor activity correlated with the transcallosal FA between both M1, while no such relation was found for mirror motor activity of the right side. Based on our study, we are not able to determine whether this null finding represents a nonexisting relationship, or whether a potential relationship is less clear and therefore below threshold. Nevertheless, the results of the correlation analysis between mirroring of the right FDI during left-hand contractions and FA of transcallosal fiber pathways does not suggest any relationship. Hence, we hypothesize that the observed difference might be related to an asymmetry in interhemispheric interactions during the exertion of unimanual movements. For example, it was previously demonstrated that the amount of IHI is asymmetrical and depends on the laterality of the movement: Duque et al. (2007) investigated premovement IHI between primary motor cortices. They found that, during movements of the dominant hand, IHI toward the contralateral (dominant) M1 decreases while it remains stable toward the ipsilateral (nondominant) M1. In contrast, during nondominant-hand movements, there was an almost constant balance in IHI toward both M1. Similarly, Newton et al. (2005) performed an fMRI study during simple unimanual movements and found a decrease in the ipsilateral M1 that was more pronounced during right-handed (dominant) movements than during left-handed movements. Taken together, these results imply that the ipsilateral M1 is subject to stronger inhibition during dominant- than during nondominant-hand movements. It has been suggested that this asymmetrical modulation of inhibition of the ipsilateral M1 plays an important role in fine motor coordination of the dominant hand. In the case of our results, it is tempting to speculate that the more fine controlled interhemispheric interactions from dominant to nondominant M1 induce a clearer pattern in parametrically increasing mirror EMG activity that, in turn, resulted in the significant relationship with brain structure. On the other hand, the relationship is potentially less clear during nondominant movements due to higher intersubject variability and therefore does not yield significance.

The specificity of our results is supported by the partial correlation analysis, demonstrating that adjacent transcallosal pathways connecting SMA or PMd are not directly related to mirror EMG activity. This is of special interest, since both SMA and PMd have dense interhemispheric connections that could also provide the biological basis for neural crosstalk and motor overflow. As mentioned above, fMRI during unimanual contractions and online EMG measurements provided evidence that SMA activation is indeed associated with mirror EMG activity (Sehm et al. 2010). However, based on the correlative nature of these findings, it remains unclear whether this correlation is driven by neural processes facilitating mirror EMG activity or whether they are operating in order to prevent mirroring. Giovannelli et al. (2006) used a virtual lesion approach with low-frequency TMS to show that downregulation of PMd led to an increase in mirror EMG activity in the right hand. They concluded that PMd forms part of a cortical network that is involved in suppressing unwanted mirror-symmetrical movements ["nonmirror-transformation network"; see also Swinnen and Wenderoth (2004)]. When considered with our current findings, it could be hypothesized that M1–M1 connections have a facilitatory influence on the basic mirror-symmetrical movement mode. Transcallosal PMd and SMA connections, in turn, might be involved in mediating the optimal amount of facilitation and inhibition between the hemispheres, thereby supporting more complex movement patterns.

Conclusions

We found that mirror EMG activity increases as a function of unimanual force of the right hand and provide new evidence that transcallosal fibers connecting bilateral M1 are associated with this phenomenon. Our data shed light on neuroanatomical structures underlying unimanual movements and a task demand-specific loss in motor selectivity.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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