

The Size of Corpus Callosum Correlates with Functional Activation of Medial Motor Cortical Areas in Bimanual and Unimanual Movements

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Effects of the size of corpus callosum measured from *in vivo* magnetic resonance imaging (MRI) recordings on cortical activations evaluated using functional MRI (fMRI) were analyzed during motor tasks. Twelve right-handed men performed unilateral finger movements and bilateral movements either with or without a temporal delay between left and right fingers. The size of the rostral part of corpus callosum and the anterior and posterior callosal truncus explained 11.9 and 15.2% of activation in the mesial frontal cortex in unimanual left and right finger movements, respectively. In bimanual simultaneous movements, 34.2% of the activated voxels in the mesial frontal cortex were related to the size of corpus callosum. In bimanual movements in which left finger movement preceded the onset of the right finger movement, the callosal size accounted for 88.7% of activation in the mesial frontal cortex. In contrast, when the right finger movement preceded the left, callosal size accounted for only 31.3% of the mesial frontal cortex activation. The correlations between callosal parameters and activation over the lateral cortex were sparse and occurred only in bimanual movements. The results suggest that corpus callosum modulates the activity of the supplementary motor and cingulate cortical areas depending on temporal complexity of bimanual movements.

Introduction

Corpus callosum (CC) represents the major cerebral commissure connecting the homotopic and heterotopic cortical regions of both hemispheres (Pandya and Seltzer, 1986; Lent and Schmidt, 1993). Lesions of CC are accompanied by apraxia (Geschwind, 1965) and a diminished temporal (Preilowski, 1972; Kennerly *et al.*, 2002) and spatial (Zaidel and Sperry, 1977; Degos *et al.*, 1987; Eliassen *et al.*, 1999) coordination of bimanual movements. The callosal connections between M1 areas are sparse (Gould *et al.*, 1986; Rouiller *et al.*, 1994). In contrast, the callosal connections between the left and right SMA are dense (Rouiller *et al.*, 1994) and contribute to bimanual coordination (Brinkman, 1980). Thus, it is expected that the size of CC is an important factor for bilateral motor control.

The relationship between size of CC and motor activity has been investigated in neurologically healthy subjects. It has been shown that the size of CC is correlated with performance in cognitive and motor tasks (Yazgan *et al.*, 1995) and with electroencephalographic measures during finger movements (Stančák *et al.*, 2000, 2002a) and following a somatosensory stimulation of the digit (Stančák *et al.*, 2002b). A larger rostral part of CC was found in musicians with early commencement of

musical training compared to musicians with later commencement or to non-musicians (Schlaug *et al.*, 1995). Since the size of CC is related to the number of myelinated and non-myelinated fibers needed for transmission of neuronal impulses and facilitation of temporal summation (Aboitiz *et al.*, 1992), the size of CC may provide information about the total capacity of the transcallosal fiber system for transmission of neuronal impulses between the homotopic motor cortical regions. We therefore hypothesized that strength of activity in the mesial motor cortex including SMA would be correlated to the size of CC. We predicted that the relationship between functional activity in motor areas and size of CC would be dependent on movement type, which is likely to be strong if movements involve temporal coordination of the left- and right-finger movements (Preilowski, 1972).

To test this hypothesis, anatomical magnetic resonance imaging (MRI) was used to measure the size of CC and functional MRI (fMRI) was used to detect increased neural activity in motor areas associated with unilateral and bilateral movements in twelve normal volunteers. Five movement tasks differing in demands on inter-hemispheric cooperation were evaluated. The correlations between the size of CC and strength of cortical activation was analyzed in primary and non-primary motor cortices.

Materials and Methods

Subjects and Procedure

Twelve healthy right-handed men (33.2 ± 11.6 years, mean \pm SD) participated in the study following written consent in accordance with institution guidelines. The selection of men into our sample was justified by gender differences in the size (Allen *et al.*, 1991; Steinmetz *et al.*, 1992) and fiber composition of CC (Aboitiz *et al.*, 1996).

The Hand-Dominanztest (Steingrüber and Lienert, 1976) was administered to verify the self-reported right-handedness. The test consisted of three motor tasks (two precision dot tapping tasks and labyrinth passing) that were performed first with the right and then with the left hand for a 15 s period. To quantify the relative performance of the right and left hand, an asymmetry index of the following form was used:

$$\text{asymmetry} = (P_{\text{right}} - P_{\text{left}}) / (P_{\text{right}} + P_{\text{left}}) \times 100$$

where P_{right} and P_{left} are the cumulative performance scores of the right and left hands, respectively. Handedness in our sample evaluated by the above method was 17.5 ± 6.3 .

The finger movement was always a brisk index finger flexion from the

initial resting, semi-stretched finger position until the index finger touched the thumb. The index finger was returned immediately to its resting position. Movements were repeated at each onset of a red light stimulus applied through LED goggles (S10VS model; Grass Instruments, Warwick, Rhode Island) that were mounted on the window of the head coil. The frequency of the light stimulus was 1 Hz. In right-finger-lead movements, the left-finger movement was started during movement of the right finger. In left-finger-lead movements, the right finger started to move during movement of the left finger. In simultaneous bimanual movements, the onsets and offsets of the right- and left-finger movements were synchronized.

The subjects were trained on the motor tasks and movements outside the magnet. Subjects practiced the conditions until the investigator was satisfied that they could follow the task instructions. This resulted in ~30 s of practice for all conditions except for the two asynchronous tapping conditions. Subjects spent 1–2 min practicing these latter two conditions. The unilateral finger movements were performed in the first MRI recording which consisted of six 1 min blocks of rest (30 s) and movements (30 s). The right- and left-finger movements alternated (e.g. rest-right–rest-left, etc.). Half of the subjects started with the right finger movements and the other half of subjects with left finger movements. One resting period (30 s) was appended to the end of the last block, thus the total recording time was 6.5 min. Two identical recordings were performed for the bimanual movements. In each of the two recordings, three types of movements alternated twice in six blocks (30 s rest, 30 s movements), e.g. simultaneous, right-finger-lead, left-finger-lead. The order of the movement types was constant for a given subject, but randomized across the 12 subjects in such a manner that each of six combinations of three types of movements occurred twice. The two recordings with bimanual movements were performed one after another with ~2 min breaks in between, during which the experimenter briefly reviewed the instructions relevant to the next recording. The hands of the subjects were continuously monitored for correct timing and side of movements. To check the subject's movements visually, the scanner room was illuminated and the subject's hands were supported by pillows. In three subjects, the first bimanual session was interrupted and re-started because the subjects performed the bimanual asynchronous movements as two separate movements or did not follow the correct order of movement tasks. In two subjects, the first recording with unimanual movements was interrupted and re-started due to spontaneous leg movements during the resting periods.

Functional and Anatomical MRI

The MR recordings were performed using a 4-T Sonata system (Siemens, Erlangen, Germany) and an open-faced head coil (Vaughan *et al.*, 2001) controlled by an *Unity* Inova console (Varian, Palo Alto, CA). The magnetic field homogeneity was optimized by manual shimming.

Two different anatomical sets were also acquired to determine the callosal size and to obtain the three-dimensional renderings of the cortical surface, respectively. At the beginning of each session, the head position was carefully adjusted using axial scout images so that the mid-sagittal plane of the head corresponded to the median plane of the MR system. For CC determination, five or six sagittal slices of 2.5 mm thickness each (field of view $25.6 \times 25.6 \text{ cm}^2$ and matrix size 256×256) were recorded using a fast-low-angle-shot sequence (FLASH; $T_R = 20 \text{ ms}$, $T_E = 5 \text{ ms}$, flip angle = 20°). For coregistration of functional and anatomical images, whole-head structural MRI was acquired using a FLASH sequence with $T_R = 10 \text{ ms}$, $T_E = 6 \text{ ms}$ and flip angle = 20° . The field of view was $22 \times 22 \text{ cm}^2$ and the matrix size was 128×128 , yielding an in-plane resolution of $1.7 \times 1.7 \text{ mm}^2$. Thirty-three axial slices of 5 mm thickness covering the whole brain were acquired. For presentation purposes (Fig. 7), anatomical images of 1 mm^3 voxel size were also acquired in one subject on a 1.5 T Siemens Magnetom Vision (Siemens, Erlangen, Germany) using a FLASH sequence ($T_R = 25 \text{ ms}$, $T_E = 6 \text{ ms}$, flip angle = 20° , slab of 18.0 cm , 180 sagittal slices, field of view $25.6 \times 25.6 \text{ cm}^2$, matrix size 256×256).

The parameters of the single-shot, gradient echo-planar imaging sequence in functional recordings were $T_R = 5 \text{ s}$, $T_E = 30 \text{ ms}$ and flip angle = 90° . The field of view was $22 \times 22 \text{ cm}^2$ and the matrix size was 64×64 , yielding an in-plane resolution of $3.4 \times 3.4 \text{ mm}^2$. Twenty axial slices of 5 mm thickness were acquired during each T_R . Images acquired during the first 10 s ($2 T_{RS}$) were discarded because magnetization had not

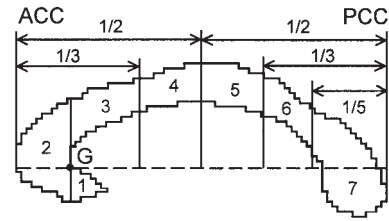


Figure 1. Evaluation of the callosal parameters according to Witelson (Witelson, 1989). Anterior border (ACC) and posterior border (PCC) define the length of the CC. The point G represents the anteriormost point of the inner convexity of the anterior CC. The line perpendicular to the ACC–PCC line which crosses the point G defines regions 1 and 2. The regions 3–7 are delineated by the vertical lines corresponding to the halves, thirds and fifths of the ACC–PCC line. The seven regions roughly correspond to the rostrum (1), genu (2), rostral truncus (3), anterior intermediate truncus (4), posterior intermediate truncus (5), isthmus (6) and splenium (7) of the CC.

yet reached steady state. Each of the recordings consisted of 78 volumes representing 6.5 min of recording time.

Size of CC

From the five sagittal MR images, the slice containing a clear view of fornix and anterior commissure was selected. The contrast of the image was enhanced using PaintShop4 software (JASC, Eden Prairie, MN) and the CC exported using the magic wand procedure of the same program. To quantify the cross-sectional mid-sagittal surface areas of particular callosal regions, such as genu, rostrum, truncus, isthmus and splenium, the method of Witelson (Witelson, 1989) was used (Fig. 1). This method has been previously implemented for measurement of the callosal size from *in vivo* MRI recordings (Steinmetz *et al.*, 1992; Jäncke and Steinmetz, 1994; Stančák *et al.*, 2000, 2002a,b). The surface areas of each of the seven callosal regions and of the total transectional callosal area were computed and used in the covariance analyses.

Statistical Parametric Mapping

SPM99 software (Department of Cognitive Neurology, Wellcome Hospital, London, UK) was used for the analysis of functional brain images. The functional images were realigned and coregistered to the first image using a robust six-body affine transformation evaluating displacements of the center-of-mass and providing a correction of motion artifacts. The time courses of the center-of-mass displacements were inspected to check for the presence of large movement artifacts. The ranges of x , y and z displacements over time in all recordings were $<1 \text{ mm}$, except for one recording in which the displacement of the center of mass in the x -axis was 1.2 mm . The functional and anatomical brain images were normalized into the standardized three-dimensional space using the MNI template, approximating the Talairach and Tournoux (Talairach and Tournoux, 1988) coordinate system. To report the cluster maxima in the Talairach coordinates, the MNI coordinates were converted to the Talairach coordinates using a conversion utility (<http://www.mrcctu.cam.ac.uk/imaging/mnispace.html>). The normalized anatomical images were used for segmentation of brain into gray and white matter and cerebrospinal fluid, and volume renderings of the cortical surface were extracted using segmented data. In the normalization step, the data were mildly smoothed to improve isotropy (3×3 kernel function) and in the next step the functional images were smoothed by a Gaussian kernel ($7 \times 7 \times 10 \text{ mm}$ full width at half maximum). The normalized and smoothed images were analyzed using the general linear model (GLM) (Friston *et al.*, 1995). The GLM analysis applies the theory of Gaussian fields to build the statistical parametric maps SPM(t), enabling evaluation of the effects of various independent variables on each and every voxel of the normalized and smoothed functional volume data. The functional volume data of each subject were scaled by the average signal intensity. Slow signal variations >2.5 cycles of activation and rest were removed using linear regression. The activations related to right-finger, left-finger, simultaneous, right-finger-leads and left-finger-leads movements were evaluated using the fixed-effect model, which is often adopted in explorations of generic aspects of functional brain architecture (Friston *et al.*, 1999). The fixed-effect, subject-separable analysis was given

advantage over the random-effect analysis since only one condition at a time and one group of subjects was evaluated, which avoided statistical problems with unequal variance encountered in between-group or between-conditions comparisons. Due to large degrees of freedom, the fixed-effect analysis was combined with conservative statistical thresholding. The activations related to right and left unimanual movements were evaluated using a single contrast design. For bimanual movements, the data from two identical recordings were analyzed conjointly using single contrasts representing simultaneous bimanual, right-finger-lead and left-finger-lead conditions. The evaluation of single effects using GLM accounted for the delay of the hemodynamic response, which was modeled by a box-car vector. In the group analysis, the P -value of 0.05 (corrected for multiple comparisons) and the spatial extent of 33 contiguous voxels were used to threshold significant activations. To analyze the influence of callosal parameters on brain activations, an analysis of covariance was applied. In the SPM covariance analysis, the mean value was subtracted from the particular callosal parameter and the contrasts in the design matrix were weighted by the centered callosal parameters. The resulting contrast image was masked by the corresponding main effect ($P = 0.05$, corrected for multiple comparisons). Since we restricted the search volume to the brain areas showing significant movement-related increase of blood oxygen level dependent (BOLD) signal, an uncorrected P -value of 0.001 and a cluster size of 33 voxels were used to threshold the covariate effects of the callosal parameters. To avoid spurious correlations due to possible outlying values in the fMRI data, the scatter plots of the individual callosal sizes and t -values were analyzed in detail. The individual t -values were measured in the spherical volumes centered at the maxima of significant covariance clusters. The diameter of the sphere varied from 6 to 12 mm for different clusters, depending on the size of the covariance maximum and on the distance of two neighboring clusters in a particular region. The normality of distributions of the t -values and of the callosal parameters was tested using the Shapiro–Wilk’s W -test (Royston, 1992) controlling for extreme values. The covariance effects based on distribution of t -values deviating significantly ($P < 0.05$) from the Gaussian distribution were cancelled. The Pearson’s correlation coefficients were computed between the individual callosal sizes and t -values for each covariance cluster. The covariance effects not yielding a significant Pearson’s correlation coefficient at 95% confidence level were not considered further. More than one-third of the significant SPM covariance clusters were discarded due to deviation from the Gaussian distribution and/or due to non-significant Pearson’s correlation coefficient. These criteria are extremely conservative.

The cerebral cortex was segmented from the skull and liquor in the original anatomical MR images under visual control of the operator using adjustable amplitude criterion. The total forebrain volume without brain stem and cerebellum was measured from the segmented anatomical data. To rule out a confounding effect of the brain volume on the callosal-size-related covariance clusters, the Pearson’s correlation coefficients between the brain volume and the t -values of the fMRI clusters were computed.

Results

The mean values and standard deviations of the sizes of the seven callosal regions and of the total callosal size are given in Table 1. To reduce the number of callosal parameters, the Pearson’s product moment correlation coefficients were computed for the sizes of seven callosal regions. Statistically significant correlations were found for all pairs from regions 4, 5 and 6 ($P < 0.05$) and, hence, these regions were combined and treated as one region. Since the size of region 1 was small (3.6% of the total callosal size), regions 1 and 2 were also combined into one region. Thus, four callosal regions were used in further analyses: rostral CC (regions 1 plus 2); anterior truncus (region 3); posterior truncus (regions 4–6); and splenium (region 7). None of these four callosal regions showed significant correlations with any other callosal region ($P > 0.05$). The correlation coefficients between the brain volume and the sizes of the

Table 1

Mean values \pm SDs of the cross-sectional mid-sagittal surface area of seven callosal regions and of the total corpus callosum ($n = 12$)

Callosal region	Mean \pm SD (mm ²)
Region 1	26.6 \pm 8.5
Region 2	170.0 \pm 34.7
Region 3	97.7 \pm 11.2
Region 4	81.9 \pm 14.9
Region 5	79.5 \pm 15.1
Region 6	66.7 \pm 13.8
Region 7	225.7 \pm 32.1
Total CC	748.0 \pm 82.7

The callosal regions are numbered from 1 to 7 according to the division of CC in Figure 1.

callosal regions were not significant ($r = 0.38$ for rostral CC, $r = -0.23$ for anterior truncus, $r = -0.17$ for posterior truncus, $r = 0.02$ for isthmus, $P > 0.05$).

Figures 2–6 show the group brain activation maps and their correlation with size of CC in the five types of movements. Activation maps are shown by projecting active clusters on three orthogonal transparent brain planes. The group activation maps obtained from the GLM analyses represented the search space in the subsequent covariance analysis. The clusters with significant covariance effects between the fMRI activation and the sizes of the rostral CC, anterior and posterior truncus of CC are shown in the *B*, *C* and *D* panels of Figures 2–6. Also, the scatter plots illustrate the relationship between the callosal parameters and the t -values in active clusters. Table 2 shows the anatomical descriptions, cluster sizes, t - or Z -values and the Talairach coordinates for each significant covariance cluster. To better visualize the covariance clusters in mesial frontal cortex in each type of movement, the fMRI clusters on the sagittal and coronal brain sections are shown in Figure 7. In addition, the vertical lines crossing the anterior and posterior cerebral commissures in the sagittal slice of the spatially normalized brain are illustrated in Figure 7*F* for separation of SMA and pre-SMA. The locations of the correlation clusters were matched with the cortical landmarks according to the atlas of cerebral sulci (Ono *et al.*, 1990). The anatomical delineation of the mesial frontal cortical regions follows the division of Vogt *et al.* (Vogt *et al.*, 1995).

Right-finger Movements

The fMRI activations were found in the contralateral M1, S1 and premotor cortex (PMC), with a major cluster maximum in the central sulcus (Fig. 2*A*). In the ipsilateral hemisphere, the inferior frontal gyrus involving the dorsal PMC showed significant activation. In the medial wall, one large cluster of activation was found with a maximum in SMA and protruding into the caudal cingulate zone (Fig. 7*A*). In addition, both ventral posterolateral nuclei of thalamus and the right superior temporal gyrus were activated (Figs 2*A* and 7*A*).

The size of the rostral CC correlated with activation in the caudal aspect of the medial frontal gyrus corresponding to SMA proper (Brodmann’s area 6*ax*; Figs 2*B* and 7*A* and Table 2*A*). The posterior truncus (Fig. 2*C*) correlated with activation in the depth of the left cingulate sulcus at half of a line connecting the anterior and posterior cerebral commissures (Brodmann’s area 24*c’g*). Figure 7*A* shows the clusters of correlated voxels and the total activation overlaid on the mid-sagittal brain slice. The voxels showing correlation with the size of CC represented 15.2% of the total volume of activation in the mesial frontal cortex.

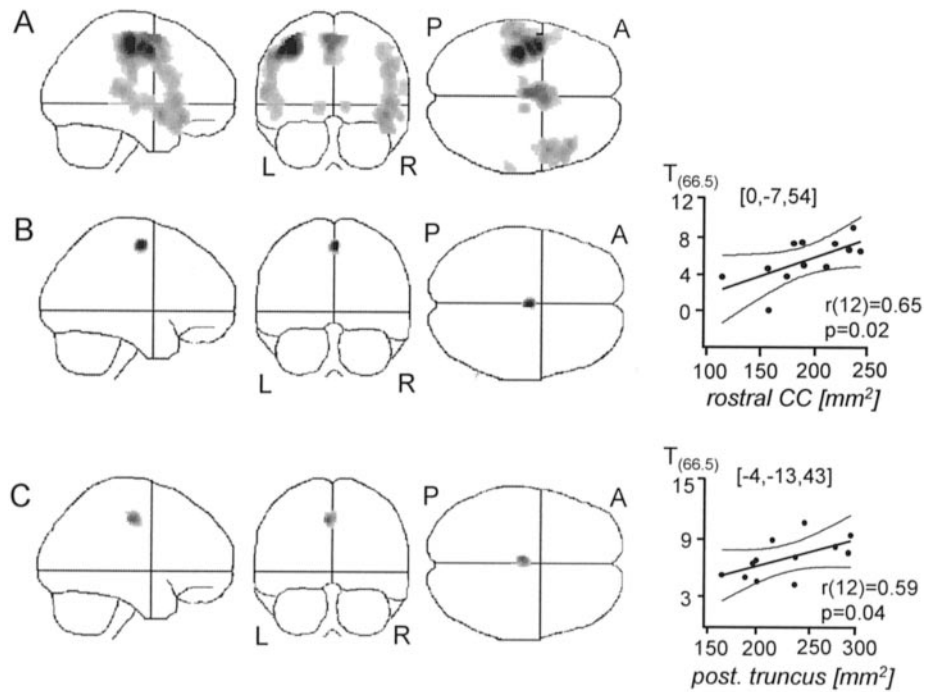


Figure 2. The fMRI activation and correlations with callosal parameters in right-finger movements. (A) The total fMRI activation obtained from the GLM analysis of 12 subjects. The activations are projected on the transparent 'glass' brains in three orthogonal views. The vertical and horizontal lines correspond to the two-dimensional projection of the medial plane and of the vertical plane crossing the anterior commissure. L, left; R, right; A, anterior; P, posterior. (B) The covariance cluster of the size of the rostral CC in SMA. The covariance cluster is shown on the transparent 'glass' brain (left panel) and as the scatter plot (right panel) of the size of rostral CC (x -axis) and t -values (y -axis) representing strength of activation in the volume centered at the respective cluster maximum. The Talairach coordinates of the covariance cluster are given in brackets. In the scatter plot, the linear regression line, the Pearson's correlation coefficient and P -value are shown. (C) The covariance cluster of the size of the posterior truncus in the cingulate cortex.

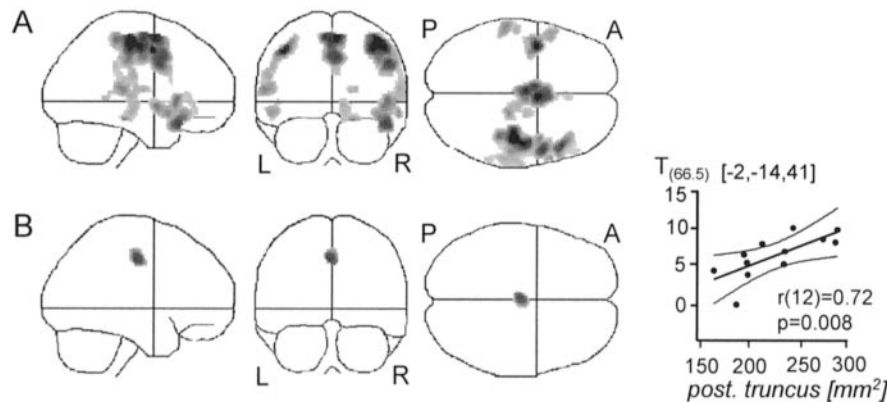


Figure 3. The fMRI activation and correlations with callosal parameters in left-finger movements. For explanation of symbols see Figure 2. (A) The total fMRI activation obtained from the GLM analysis. (B) The covariance cluster representing the correlation between the size of the posterior truncus of CC and functional activation in the cingulate cortex.

Left-finger Movements

In the left-finger movements (Figs 3A and 7B), the contralateral M1, S1 and PMC of the precentral and medial frontal gyri showed the largest activations on the lateral surface of the hemispheres. Over the ipsilateral hemisphere, the premotor cortex, the inferior frontal gyrus and S1 were activated. On the medial wall of hemispheres, SMA and the caudal cingulate cortical zone showed the largest activation (Fig. 7B). However, significant activation was also found rostrally to the vertical plane crossing the anterior commissure corresponding to pre-SMA and to the rostral cingulate cortical zone. The right ventral posterolateral nucleus of thalamus and the right and left superior temporal

gyrus involving secondary somatosensory cortex (S2) were also activated.

The only callosal parameter manifesting a significant relationship with functional activation was the posterior truncus. The correlation cluster was located in the left cingulate sulcus, about halfway between the anterior and posterior cerebral commissures (Figs 3B and 7B and Table 2B). The voxels showing a significant correlation with callosal parameters accounted for 11.9% of the total volume of activation in the mesial frontal cortex.

Together, the results of the left- and right-finger tasks suggest that correlations between the size of CC and fMRI activation in unimanual movements occur only in the mesial frontal cortex.

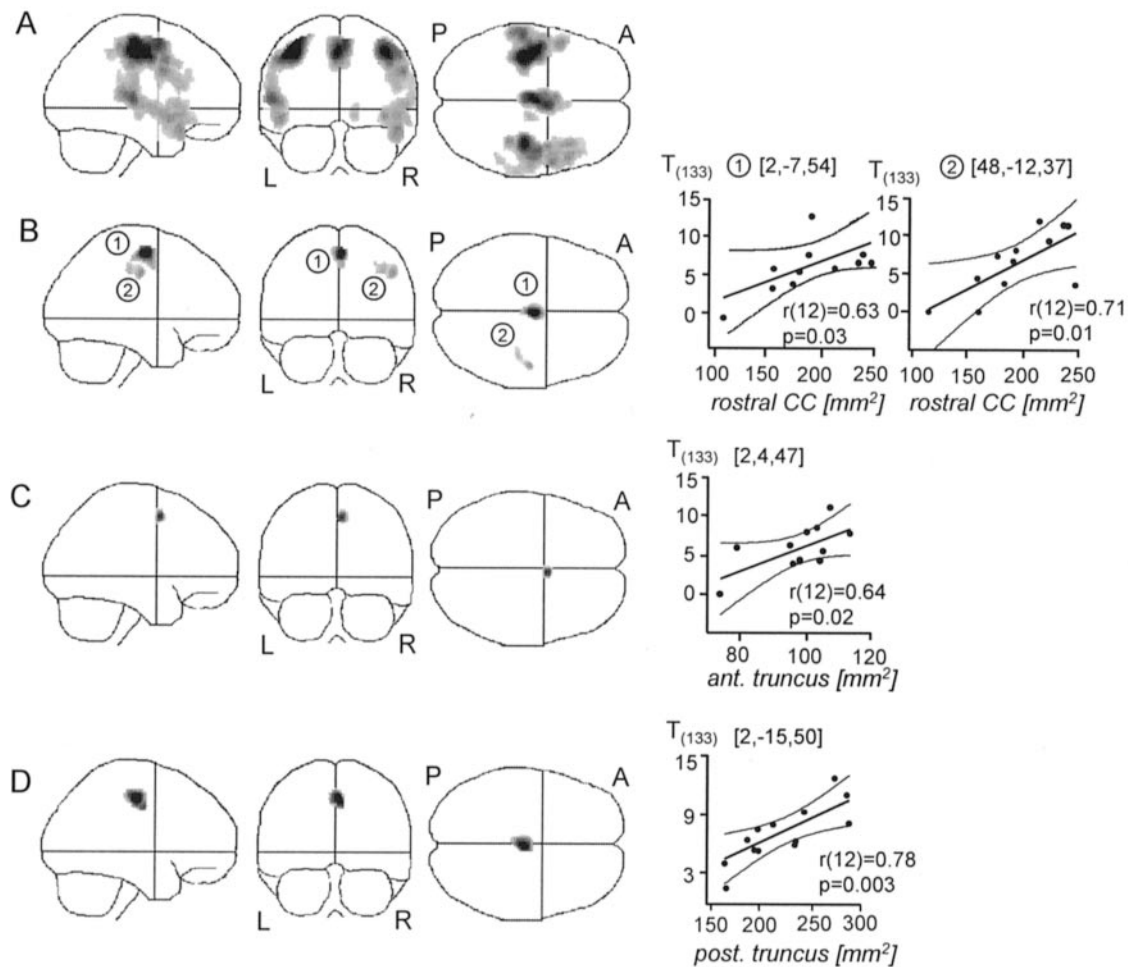


Figure 4. The fMRI activation and correlations with callosal parameters in bimanual simultaneous movements. For explanation of symbols see Figure 2. (A) The total fMRI activation obtained from the GLM analysis. (B) The covariance clusters of the size of the rostral CC in SMA (1) and in the right M1 (2). The cluster numbers in the transparent brains correspond to the numbering of the scatter plots. (C) The covariance cluster of the size of the anterior truncus of CC in the cingulate cortex. (D) The covariance effects of the size of the posterior callosal truncus in SMA.

Bimanual Simultaneous Movements

Simultaneous right- and left-finger movements were associated with activations in the left and right M1 and PMC, and in the right inferior frontal gyrus over the lateral surface of the hemispheres (Fig. 4A). In addition, activations were found in S1 and in the right inferior parietal lobule. In the medial walls of the hemispheres, the areas caudal and rostral to the vertical plane crossing the anterior commissure showed distinct activations (Fig. 7C). Additional activation foci were found in the right subthalamic nucleus and in the right superior temporal gyrus including S2 in the upper bank of the Sylvian fissure.

The rostral CC (Fig. 4B) and both the anterior (Fig. 4C) and posterior truncus (Fig. 4D) showed distinct correlations with the fMRI clusters in the mesial frontal cortex (Fig. 7C). The rostral CC correlation cluster was located in the caudal part of the medial frontal gyrus corresponding to Brodmann's area 6 α , representing the SMA proper (Table 2C). Another SMA cluster, located at the boundary of the medial frontal gyrus and the paracentral lobule in Brodmann's area 6 α , correlated with the size of the posterior callosal truncus. The correlation cluster related to the size of the anterior truncus was found in the cingulate sulcus a few millimeters rostral to the vertical plane transversing the anterior cerebral commissure (Brodmann's area

24c'). Of the activated voxels in the mesial frontal cortex, 34.2% showed a covariation with callosal parameters.

The covariate effects over the lateral cortex (Table 2C and Fig. 4B) were found between the size of the rostral CC and fMRI activity in the right anterior bank of the central sulcus and over the omega-shaped portion of the precentral gyrus corresponding to hand M1 (Yousry *et al.*, 1997). The volume of activation in the lateral cortex showing correlation with callosal size was only 1.2% of the total activation.

Bimanual Right-finger-lead Movements

The activation patterns observed during the right-finger-lead movements were similar to simultaneous movements and involved both M1 and PMC, anterior parietal cortex and the right prefrontal cortex (Fig. 5A). In the medial walls of hemispheres, SMA showed the largest activation, but two additional cluster maxima were observed in the cingulate cortex rostral to the vertical plane crossing the anterior commissure (Fig. 7D). Additional activations were found in the right thalamic ventral posterolateral nucleus and both parahippocampal gyri.

The clusters showing correlations with the size of the rostral CC were found in the caudal part of the medial frontal gyrus corresponding to SMA proper (Brodmann's area 6 α ; Figs 5B

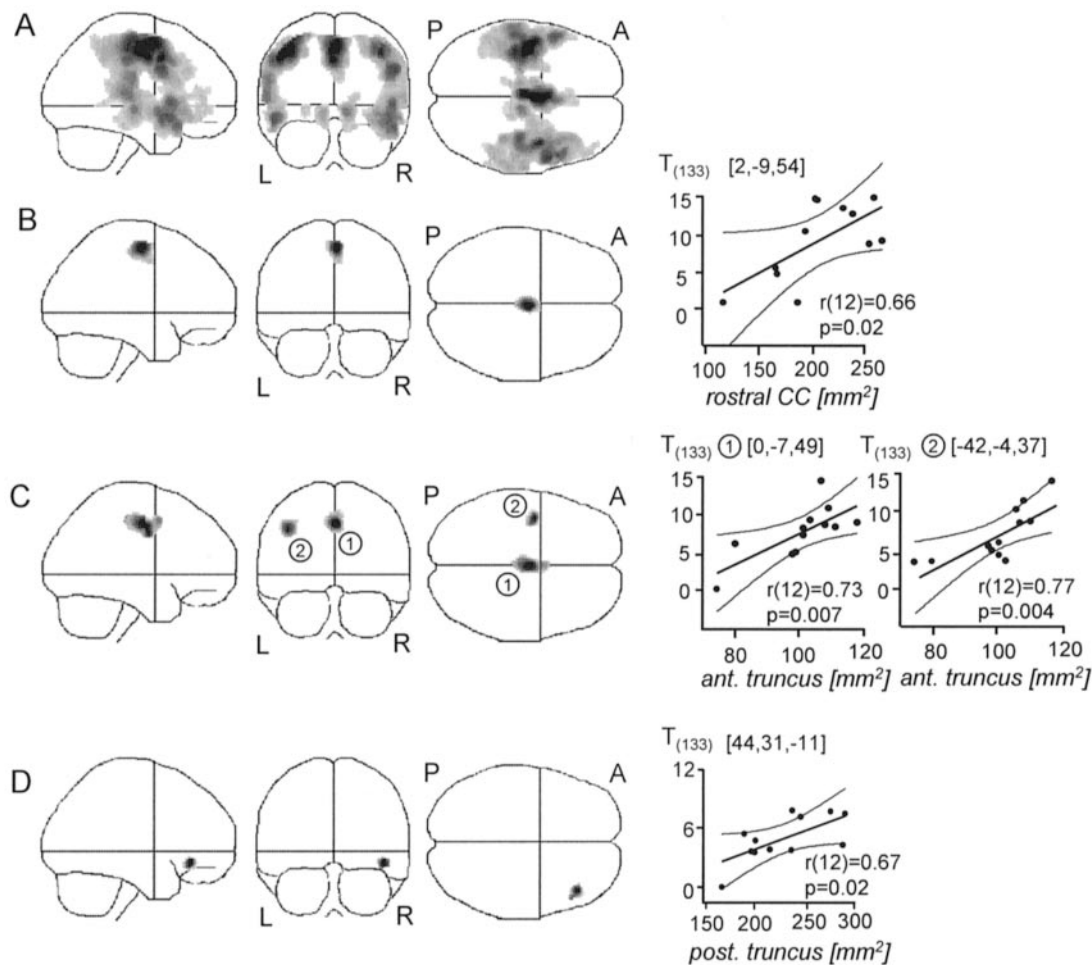


Figure 5. The fMRI activation and correlations with callosal parameters in bimanual right-finger-lead movements. For explanation of symbols see Figure 2. (A) The total fMRI activation obtained from the GLM analysis. (B) The covariance effects of the size of the rostral CC in SMA. (C) The covariance clusters of the size of the anterior truncus of CC in the cingulate cortex (1) and left M1 (2). (D) The covariance effects of the size of the posterior callosal truncus in the right prefrontal cortex.

and 7D and Table 2D). The anterior truncus showed a distinct cluster of significantly correlated voxels in the cingulate sulcus a few millimeters caudal from the vertical plane crossing the anterior commissure (Brodmann's area 24c'g). These two clusters accounted for 31.3% of the activated voxels in the mesial frontal cortex during right-finger-lead movements. Over the lateral cortex, the size of the anterior truncus correlated with activation in the left precentral gyrus corresponding to hand M1 region (Fig. 5C) and the size of the posterior truncus with a cluster in the orbito-triangular part of the right inferior frontal gyrus (Brodmann's area 47; Fig. 5D). The clusters showing correlations with callosal size represented 1.7% of the activated voxels in the lateral cortex.

Bimanual Left-finger-lead Movements

The fMRI activations over the lateral cortex in left-finger-lead movements involved the left and right M1, S1, PMC, the inferior parietal lobules and both superior temporal gyri, including S2 regions (Fig. 6A). In the medial walls, SMA and the caudal cingulate and rostral cingulate zones were activated (Fig. 7E). Finally, the left and right ventral posterolateral thalamic nucleus and left putamen showed significant activation.

In the mesial frontal cortex, the size of the rostral truncus (Fig. 6B) correlated with a large cluster of activated voxels in the medial frontal gyrus, both rostral and caudal from the vertical

plane crossing the anterior commissure corresponding to Brodmann's areas 6a β and 6a α , respectively (Table 2E and Fig. 7E). The sizes of the anterior and posterior truncus correlated with activations in the cingulate cortex (Fig. 6C,D, respectively). The anterior truncus cluster was located in the cingulate cortex ~7 mm posterior from the vertical plane crossing the anterior commissure (Brodmann's area 24 c'g) and the posterior truncus correlation cluster was situated 8 mm caudal and 4 mm dorsal relative to the former correlation cluster (Brodmann's area 23c). As much as 88.7% of activated voxels in the mesial frontal cortex showed a significant covariation with the size of CC.

In the lateral cortex, the rostral CC correlated with a cluster of activation in the right prefrontal cortex and in the left inferior parietal lobule (Fig. 6B and Table 2E). The prefrontal cortex cluster was located in the *pars orbitalis* of the inferior frontal gyrus (Brodmann's area 47). The location of the inferior parietal lobule cluster was a few millimeters medial and posterior from the intersection of the postcentral and interparietal sulci. A cluster of voxels showing a significant correlation with the size of the anterior truncus was observed in the left superior temporal gyrus, close to the cross-section of the extension of the central sulcus and the lateral cerebral fissure. For the size of the posterior truncus, the clusters in the left premotor cortex and in the left Sylvian fissure showed significant correlations. The premotor cortex correlation cluster was situated in the dorsal

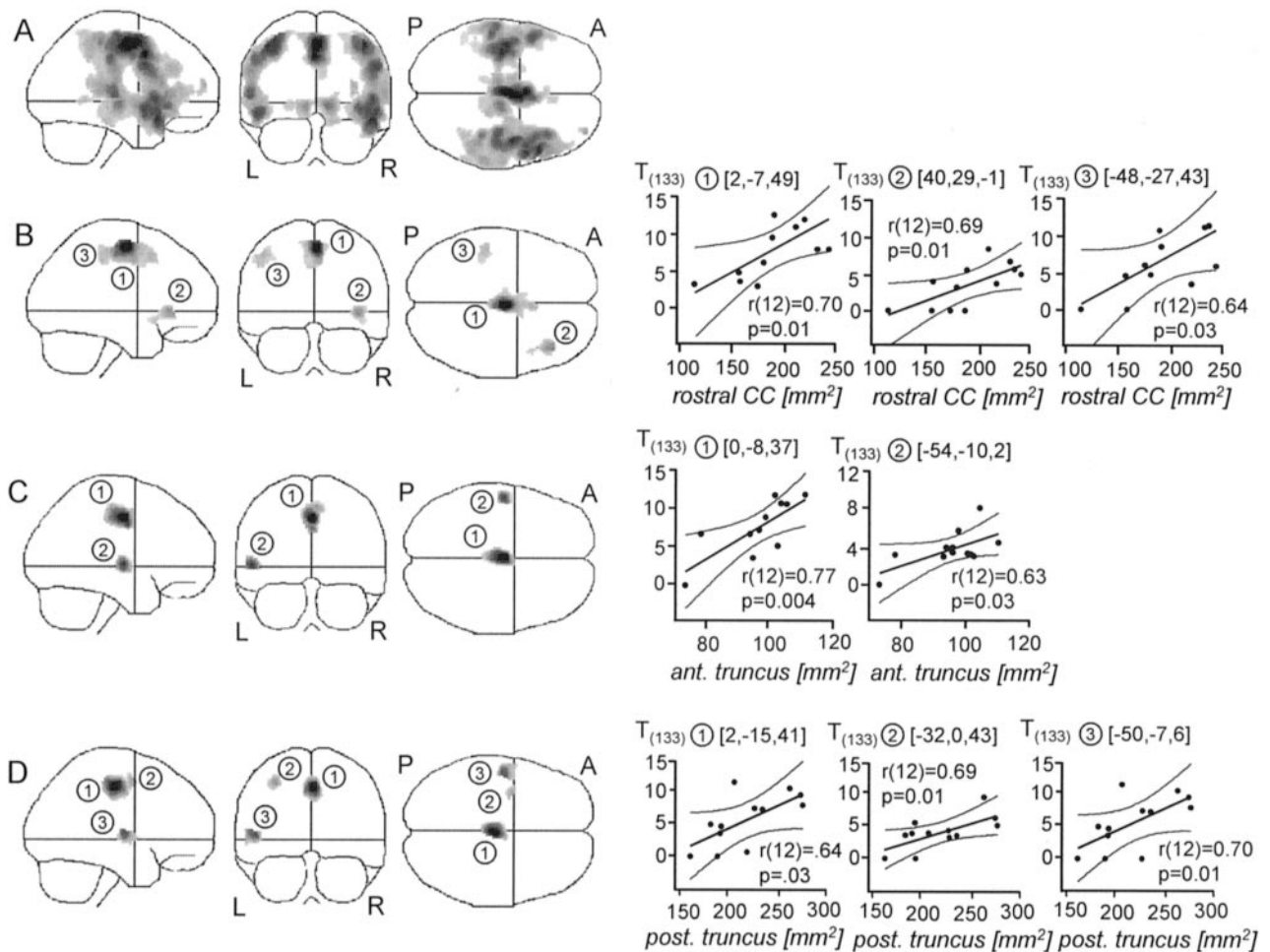


Figure 6. The fMRI activation and correlations with callosal parameters in bimanual left-finger-lead movements. (A) The total fMRI activation obtained from the GLM analysis. (B) The covariance clusters of the size of the rostral CC in SMA (1), right prefrontal cortex (2) and left inferior parietal lobule (3). (C) The covariance effects of the size of the anterior truncus of CC in the cingulate cortex (1) and left temporal cortex (2). (D) The covariance effects of the size of the posterior callosal truncus in the cingulate cortex (1), premotor cortex (2) and S2 (3).

aspect of the intermediate frontal gyrus, close to the precentral sulcus. The correlation cluster in the left Sylvian fissure was located in the depth of the Sylvian fissure at the level of the central sulcus, which corresponds to S2 cortex. These clusters occupied 4.1% of the total volume of activation in the lateral cortex.

The Pearson's correlations between the brain volume and the *t*-values of the clusters showing correlations with callosal size were not significant in any of the five types of movements ($P > 0.05$). The correlation coefficients were mild and negative ($-r = -0.2$) for most of the clusters. Thus, the correlations between the size of CC and fMRI activation could not be attributed to the brain volume.

Discussion

We analyzed the correlations between the callosal size and fMRI activation in unimanual and bimanual movements with different demands on the coordination of the left and right finger movements. Since volume of activation in fMRI studies is closely related to the statistical threshold used, the volume of activation correlated with callosal size will also vary in parallel with the statistical threshold. However, our major findings referring to relative volumes of correlation clusters in the mesial frontal

cortex in different types of movements and to the proportion of callosal correlations in the medial and lateral cortex are independent of the statistical threshold. The correlations between the sizes of the four callosal regions and the forebrain volume were not significant. The lack of statistically significant correlations between brain volume and callosal size can be attributed to the small number of subjects in the present study compared to previous studies, which reported a small positive correlation between the size of CC and brain volume (Witelson, 1989; Jäncke *et al.*, 1997).

Mesial Frontal Cortex and the Size of CC

Bimanual movements are associated with enhanced activation of SMA (Toyokura *et al.*, 1999; Jäncke *et al.*, 2000), especially if a motor task requires bimanual coordination (Sadato *et al.*, 1997; Goerres *et al.*, 1998; Toyokura *et al.*, 1999). Electrical stimulation of SMA neurons produces bilateral limb movements (Tanji *et al.*, 1988; Wiesendanger *et al.*, 1996). Other studies have questioned the role of SMA in bimanual coordination (Kermadi *et al.*, 1997; Kazennikov *et al.*, 1999). SMA of both hemispheres show dense callosal connections (McGuire *et al.*, 1991; Rouiller *et al.*, 1994), which may contribute to bimanual coordination. A unilateral SMA lesion in monkeys impairs coordination of bimanual movements (Brinkman, 1980). During

Table 2

The anatomical descriptions, the Talairach x , y , z (mm) coordinates, Z -values of significant cluster maxima and numbers of activated voxels of callosum-related activation in (A) right-finger, (B) left-finger, (C) simultaneous, (D) right-finger-lead and (E) left-finger-lead movements

Anatomical description	x	y	z	Z/t^a	Voxels
A. Callosum-related activations in right finger movements					
Rostral CC					
Medial frontal gyrus (SMA)	0	-7	54	4.8	77
Posterior truncus					
Left cingulate sulcus	-4	-13	43	4.5	99
B. Callosum-related activations in left finger movements					
Posterior truncus					
Left cingulate gyrus	-2	-14	41	5.0	184
C. Callosum-related activations in simultaneous bimanual movements					
Rostral CC					
Right medial frontal gyrus (SMA)	2	-7	54	7.0	239
Right precentral gyrus	48	-12	37	4.4	81
Anterior truncus					
Right cingulate sulcus	2	4	47	4.0	58
Posterior truncus					
Right medial frontal gyrus	2	-15	50	5.6	246
D. Callosum-related activations in right-finger-lead bimanual movements					
Rostral CC					
Right medial frontal gyrus (SMA)	2	-9	54	8.8*	307
Anterior truncus					
Cingulate gyrus	0	-7	41	6.7	517
Left precentral gyrus	-42	-4	37	6.0	159
Posterior truncus					
Right inferior frontal gyrus	44	31	-11	7.3	59
E. Callosum-related activations in left-finger-lead bimanual movements					
Rostral CC					
Right medial frontal gyrus (SMA)	2	-7	49	10.3*	832
Right inferior frontal gyrus	40	29	-1	5.8	134
Left inferior parietal lobule	-48	-27	43	4.4	145
Anterior truncus					
Cingulate gyrus	0	-8	37	6.8	725
Left superior temporal gyrus	-54	-10	2	5.7	161
Posterior truncus					
Right cingulate sulcus	2	-15	41	8.2*	432
Left intermediate frontal gyrus	-32	0	43	4.7	45
Left Sylvian fissure (S2)	-50	-7	6	6.5	135

The clusters of correlated activations are grouped according to callosal regions (rostral CC, anterior truncus, posterior truncus). In the Talairach coordinate system, negative values of the left-right axis (x) indicate left hemisphere and negative values of the antero-posterior axis (y) indicate locations caudal to the vertical plane crossing the anterior commissure. The values of the vertical z -axis in millimeters increase from the base to the top of the cerebrum.

*If the Z -value attained was infinite, the t -value was applied.

^aFor A and B, $t = t(799.5)$; for C-E, $t = t(1599)$.

bimanual movements performed by the monkey, the hands moved in parallel rather than in a complementary and supportive fashion. This deficit is eliminated by subsequent callosal section, indicating that the intact SMA controlled the lesioned SMA via callosal fibers. The correlations between callosal size and SMA activation observed in the present study fit with the callosotomy findings in monkey (Brinkman, 1980).

The callosum size correlations were observed also in the cingulate cortex in unimanual right-finger movements and in all types of bimanual movements. Callosal connections between the left and right cingulate cortex have been reported in the rat (Jacobson, 1970), cat (Matsunami *et al.*, 1994), monkey (Pandya and Seltzer, 1986) and human (Locke and Yakovlev, 1965), suggesting biological value of the callosal connections for the cingulate cortex functions. Stephan *et al.* (Stephan *et al.*, 1999) found that a patient with a lesion in the anterior cingulate cortex had impaired bimanual coordination and diminished fMRI activation of the anterior cingulate cortex, especially during

bimanual movements involving temporal asynchrony of left- and right-hand movements. In spite of anatomical and functional differences of various motor areas in the mesial frontal cortex (Vogt *et al.*, 1995; Zilles *et al.*, 1995; Picard and Strick, 1996), the mesial frontal cortex appears to represent a functional unity which allows flexible participation of various mesial motor areas in the motor task. The recruitment of callosal fibers obviously contributes to the integration of the left and right mesial frontal cortex capable of eliciting right or left unilateral or bilateral movements (Tanji *et al.*, 1988).

Two correlation clusters in the cingulate cortex observed in bimanual left-finger-lead movements were located in the rostro-caudal axis, roughly paralleling the course of the cingulate sulcus (Fig. 7E). The more rostral of the two correlation clusters was related to the size of the anterior truncus and the caudal cluster referred to the size of posterior truncus. Since the corticotopy of the callosal fibers follows the rostro-caudal order of various cortical regions, including the cingulate cortex (Pandya and

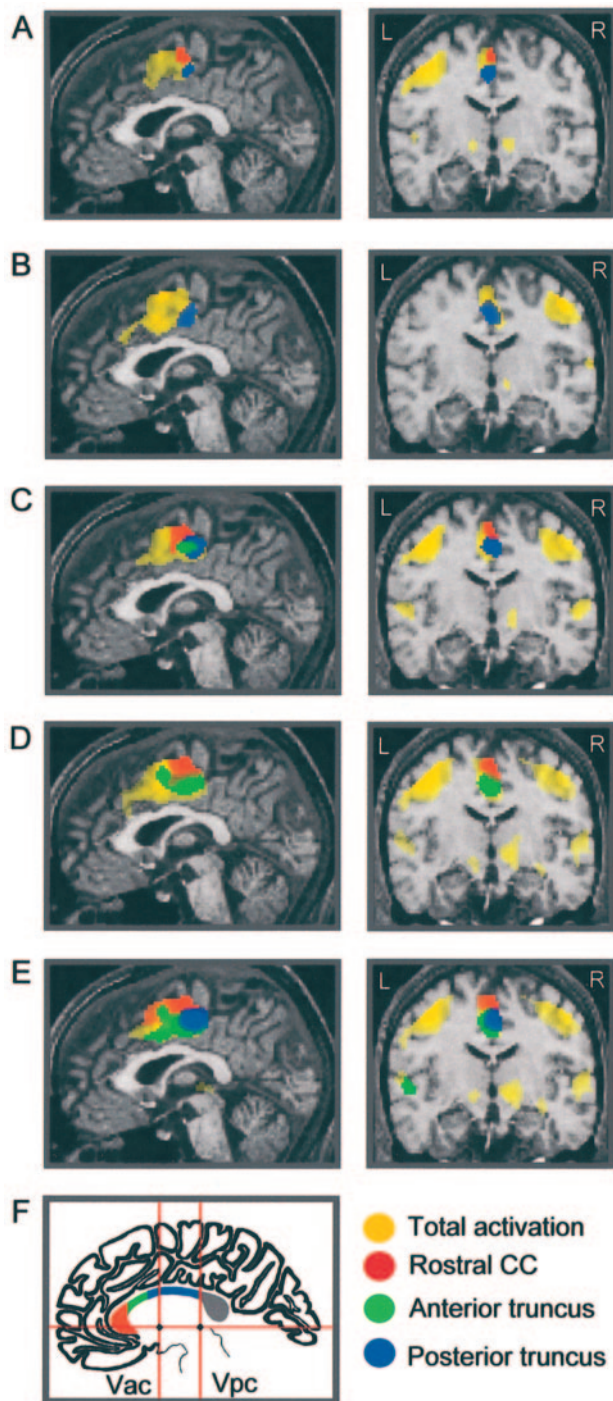


Figure 7. The total mesial cortical activation (yellow) and the activations showing significant covariation with the rostral CC (red), anterior truncus (green) and posterior truncus (blue) in (A) right finger, (B) left finger, (C) bimanual simultaneous, (D) bimanual right-finger-lead and (E) bimanual left-finger-lead movements. The sagittal and coronal slices are shown. (F) Illustration of the medial cortical surface and vertical planes crossing anterior commissure (Vac) and posterior commissure (Vpc). The callosal regions corresponding to the rostral CC, anterior and posterior truncus are filled with red, green and blue colors, respectively. L, left; R, right. The coronal sections in panels (A–E) correspond to the plane $y = -14$ mm; the lateral views correspond to the paramedian plane of $x = 2$ mm.

Seltzer, 1986; Matsunami *et al.*, 1994), the pattern of correlations in the cingulate cortex can be attributed to the rostro-caudal arrangement of callosal fibers.

The large extent of callosal activity in the mesial frontal cortex during left-finger-lead movements compared to simultaneous or right-finger-lead movements may refer to additional effort to overcome hand dominance manifesting, for instance, in the right-hand lead during simultaneous bimanual movements (Viviani *et al.*, 1998). Although the right-finger lead might be smaller in bimanual stereotyped repetitive finger movements compared to a trajectory drawing movement task, the prominent callosal-size-related activation in left-lead movements is likely to be attributed to hand dominance effects. Interestingly, tasks involving a cognitive conflict, such as the Stroop word-color test, strongly activate the anterior cingulate cortex (Pardo *et al.*, 1990).

A relatively weak callosal size correlation in the mesial frontal cortex activation was observed in unimanual movements. SMA (Tanji *et al.*, 1988; Ball *et al.*, 1999; Erdler *et al.*, 2000) and the anterior cingulate cortex (Shima *et al.*, 1991; Ball *et al.*, 1999) are activated during the preparatory period preceding a simple unimanual movement. The coupling of cortical oscillations between SMA and M1/S1 increases during movement (Ohara *et al.*, 2001) and the strength of M1/S1-to-SMA coupling is proportional to the size of callosal truncus (Stančák *et al.*, 2002a). It is thus likely that the callosal-size-related activation in the mesial frontal cortex contributes to the balance of the background activation in the left and right M1.

Lateral Cortex Activation and the Size of CC

Under the adopted statistical criteria, there were no correlation clusters in lateral cortex in unimanual movements and the volume of total activation represented by the clusters correlated with the callosal size was only 1–4% in bimanual movements. Since the statistical evaluation of correlation clusters was identical in all cortical regions, the sparse occurrence of correlations in the lateral as compared to medial cortex cannot be explained by statistical thresholds. The sparse occurrence of correlation clusters in M1 and premotor cortex during unimanual movements fits with the lack of differences between acallosal and normal subjects in fMRI activation over the primary motor areas (Reddy *et al.*, 2000).

The correlation clusters occurred in M1, premotor cortex, prefrontal cortex, S2 and temporal cortex and in inferior parietal lobule in bimanual movements. The present study cannot fully explain the precise neurophysiological origin of the correlation clusters in the lateral cortex. Two alternative mechanisms could be considered.

First, the neuronal impulses originating in M1 are relayed through the homotopic and non-homotopic (Pandya and Vignolo, 1969; Jenny, 1979) callosal fibers to the motor, premotor and prefrontal cortical regions of the opposite hemisphere. This explanation is supported by transcranial magnetic stimulation studies showing activation of the frontal cortex contralateral to the stimulated M1 (Fox *et al.*, 1997; Siebner *et al.*, 2001; Komssi *et al.*, 2002). The spread of neuronal impulses through the callosal fiber system would be proportional to the size of CC, especially of the callosal truncus which contains the large-diameter callosal fibers (Aboitiz *et al.*, 1996) connecting M1 and SMA regions of both hemispheres. Via direct homotopic and heterotopic callosal connections with M1, the motor areas over the lateral surface of cerebral hemisphere can be tuned.

An alternative explanation would be that the activation which originates in the mesial frontal cortex prior to voluntary movement is built up on the basis of the callosal connections. The strength and spatial extent of the mesial frontal cortex activation would be proportional to the size of CC, as shown in

the present study. Since SMA radiate to multiple areas of the lateral cortex involving M1, PMC and prefrontal cortex (Pandya and Kuypers, 1969; Wang *et al.*, 2001), the size of CC would indirectly contribute to the activation of the lateral cortex. The cingulate cortex has neuronal connections with the motor regions on the medial and lateral surfaces of the hemispheres and with the prefrontal cortex (Devinski *et al.*, 1995; Paus, 2001). The anterior cingulate region close to the vertical plane transversing the anterior cerebral commissure, which showed the most intense callosal size correlations, corresponds to the motor zone in Brodmann's area 24c'g and contains large pyramidal cells in layer V projecting to the spinal cord (Braak, 1976). The correlations between the size of CC and activations in the cingulate and in the prefrontal cortex are likely due to callosally mediated activation in the cingulate cortex and subsequent activation of the prefrontal cortex on the basis of association fibers between the cingulate and prefrontal cortices (Barbas and Pandya, 1989; Bates and Goldman-Rakic, 1993). Koski and Paus (Koski and Paus, 2000), in their meta-analysis of positron emission tomography (PET) studies, reported frequent co-occurrence of activations in the cingulate and prefrontal cortex. Hypothetically, since the cingulate cortex radiates to the prefrontal cortex (Barbas and Pandya, 1989; Bates and Goldman-Rakic, 1993) and to M1 (Muakkasa and Strick, 1979), the activation in the prefrontal cortex and M1 may first arise in the cingulate cortex of one hemisphere and spread further through the callosal fibers to the opposite cingulate cortex and, subsequently, to the prefrontal cortex and M1.

The hypothesis stressing the role of the callosal connections between the mesial frontal cortex regions of both hemispheres is favored by the findings of an early premotor activation in these cortical regions, preceding the M1 activation (Tanji *et al.*, 1988; Shima *et al.*, 1991; Ball *et al.*, 1999; Erdler *et al.*, 2000). The preparatory neuronal activation might be decisive for elaboration of a motor plan of bimanual coordination, especially if movements involve precise temporal matching of the left- and right-hand movements. Future studies combining the transcranial magnetic stimulation of M1 or SMA with an analysis of the callosal size correlations could shed more light on the role of CC in activation of motor cortical areas.

From a neurobehavioral perspective, CC appears to possess a large residual capacity for tuning the medial and lateral motor cortical regions, which is only slightly used during unimanual movements. However, if bimanual movements involve temporal complexity and are led by the non-dominant hand, the callosal fiber system is switched on to coordinate especially the activation of the right and left SMA and cingulate cortex. Our study emphasizes the role of the mesial frontal cortex in bimanual coordination and provides an empirical basis for neurophysiological interpretation of impaired bimanual coordination in patients with callosal dysfunctions. The size of the anterior CC and callosal truncus showed correlations with functional activation in the present study. Lesions of posterior CC are associated with impaired spatial coordination of bimanual movements (Degos *et al.*, 1987; Eliassen *et al.*, 1999). It can be conjectured that anterior regions of CC are related to temporal coordination and posterior callosal regions to spatial coordination of bimanual movements. Future studies should address the role of callosal size in functional activation during motor tasks necessitating spatial coordination of bimanual movements.

The correlations between cerebral activation and size of CC point to the activation of commissural pathways during motor tasks. However, since the results are based on the correlation

analysis, it is difficult to infer the causal relationships in the sense that a particular cortical activation is mediated solely by the callosal connections. The results should apply to all tasks requiring interhemispheric communication. This could include bimanual movements, unimanual movements (due to ipsilateral cortex activation) and potentially tasks such as a left-handed response to a stimulus presented in the right visual field.

Notes

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