

# The role of anterior cingulate cortex and precuneus in the coordination of motor behaviour

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## Abstract

Behavioral studies in humans have shown that bimanual coordination imposes specific demands on the central nervous system that exceed unimanual task control. In the present study we used functional magnetic resonance imaging to investigate the neural correlate of this additional coordination effort, i.e. regions responding more strongly to bimanual movements than inferred from summing up the responses to the unimanual subtasks. Subjects were scanned while performing movements along different directions, either uni- or bimanually. During the bimanual condition, trajectories of movement of the left and right hand were spatially incompatible, such that additional effort was required to break away from intrinsically favored mirror-movements and to integrate movements of both limbs into a new spatial pattern. Our main finding was that the execution of spatially complex bimanual coordination as compared with the unimanual subtasks activated the anterior cingulate cortex (posterior part) as well as the dorso-anterior precuneus. We hypothesize that the anterior cingulate exerts its modulatory effect on other motor areas, such as the primary motor cortex and the supplementary motor area, in order to suppress intrinsically favored coordination tendencies. Conversely, the precuneus is likely to be involved in shifting attention between different locations in space, which was necessary for monitoring the trajectories of the left and right wrist when both limbs moved in parallel. Our findings suggest that the coordination effort during bimanual and perhaps other modes of coordinated behavior is mediated by regions contributing to higher order functions, which form an interface between cognition and action.

## Introduction

Bimanual movements can become extremely challenging when the left and the right limb have to perform two different tasks in parallel, such as drawing a triangle with one hand and a circle with the other hand. Even when the unimanual subtasks are easily executed in isolation, movement performance can decrease substantially when they are combined in a bimanual setting (Kelso *et al.*, 1979; Swinnen & Walter, 1991; Kaluzny *et al.*, 1994; Kelso, 1995; Muri *et al.*, 1999; Swinnen *et al.*, 2001; Swinnen, 2002; Wenderoth *et al.*, 2003; Swinnen & Wenderoth, 2004). As such, interlimb coordination is not simply the ‘sum of the parts’, but requires additional computational resources to integrate the limbs’ movements into a common spatiotemporal pattern. These specific demands on the central nervous system differ from single limb task control and reflect the additional coordination effort. The coordination effort depends not only on the bimanual nature of the task but also on the spatiotemporal compatibility of the subtasks. Whereas symmetric bimanual actions (e.g. inward circling with both hands) are highly compatible and are executed with great ease, nonsymmetric actions (e.g. circling with the left hand while drawing a triangle with the right hand) are considered to be more complex owing to their lower degree of compatibility, requiring some additional effort to prevent the emergence of interlimb interference. In particular, spatial interference is reflected by the mutual assimilation of movement direction or amplitude of both hands and indicates

difficulties in interhemispheric spatial integration (Franz *et al.*, 1991; Spijkers & Heuer, 1995; Swinnen *et al.*, 2001). In summary, the coordination effort arises in the first instance from performing bimanual vs. unimanual movements but depends additionally on the degree of compatibility between the bimanual subtasks.

The neural correlates of the coordination effort can be identified by functional imaging methods. Previous studies applied functional magnetic resonance imaging (fMRI) or positron emission topography (PET), while subjects performed bimanual vs. unimanual finger/hand movements (Sadato *et al.*, 1997; Goerres *et al.*, 1998; Stephan *et al.*, 1999a,b; Toyokura *et al.*, 1999, 2002; Jancke *et al.*, 2000; Tracy *et al.*, 2001; Nair *et al.*, 2003). In most studies, the observed differences between coordinated vs. single limb performance were highest when nonsymmetric actions were required (e.g. antiphase movements). This comparison frequently revealed an increased activation in the supplementary motor area (SMA) (Sadato *et al.*, 1997; Goerres *et al.*, 1998; Toyokura *et al.*, 1999, 2002; Jancke *et al.*, 2000; Tracy *et al.*, 2001; Nair *et al.*, 2003).

However, only limited conclusions can be drawn from many of these imaging studies, because bimanual and unimanual conditions were not directly contrasted, or bimanual movements were compared with movements with the dominant hand only. Moreover, relatively simple bimanual tasks were used, whereas it was shown recently that some ‘coordination areas’ only become detectable by functional imaging methods when the coordination complexity of the bimanual condition is sufficiently high (Debaere *et al.*, 2004; Wenderoth *et al.*, 2004b). Accordingly, the brain activations associated with the coordination effort during interhemispheric spatial integration are still

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elusive. Therefore, in the present study, we aimed at identifying brain areas that reflect the coordination effort arising from the interhemispheric integration of different movement directions during bimanual actions. For this purpose, we combined fMRI and a well-known psychophysical paradigm, namely the so-called line-star drawing task (Swinnen *et al.*, 2001, 2002; Wenderoth *et al.*, 2003), requiring subjects to trace lines with different orientations, either uni- or bimanually. Based on previous research (see studies cited above), we hypothesized that the coordination effort is reflected by areas involved in spatial planning, the control of interhemispheric information interchange, or the suppression of preferred response tendencies. These functions are likely to be located in superior parietal–dorsal premotor areas, particularly midline structures such as the cingulate cortex.

## Materials and methods

### Subjects

Five male and five female volunteers aged  $25 \pm 5$  years (mean  $\pm$  SD) participated in the experiment. All were right-handed (Oldfield, 1971), naïve with respect to the task and had normal vision. None of them participated in regular musical training. Before participating in the experiment, all subjects gave written informed consent to participate in the study, which was approved by the Ethics Committee of Biomedical Research at K.U.Leuven in accordance with the Declaration of Helsinki (1964). Subjects were paid for their services.

### Experimental setup

Subjects lay supine in the scanner with their upper arms next to the body and their forearms in a nearly vertical position, i.e. the elbow was flexed at an angle between  $90^\circ$  and  $135^\circ$  (Fig. 1A). On a display in front of them, task instructions were projected by a LCD projector (Barco 6300,  $1280 \times 1024$  pixels). Subjects operated with each wrist a two-dimensional joystick, which was freely movable (no spring loading). The joysticks were manufactured in-house, each utilizing two fMRI-compatible, optical encoders (Hewlett-Packard, Malaysia; spatial resolution of  $0.18^\circ$ ) to register movements along the vertical and horizontal dimension (sampling rate, 100 Hz). Head movements were restricted by a bite-bar as well as two cushions mounted to the left and right side of the head.

### Behavioral tasks

During scanning, subjects performed rhythmical ‘line drawing’ and ‘star drawing’ subtasks either uni- or bimanually (Fig. 1B). Previous work using this complex coordination paradigm has shown that, even though the subtasks are simple, their bimanual performance necessitates a high level of on-line monitoring and control during the spatial integration of directionally incompatible movements. Thus, subjects cannot rely on pre-existing coordination patterns but have to develop a new coordination strategy from scratch. As a prerequisite, they have to inhibit the strong tendency of performing mirror-symmetric movements. A more extensive description of the tasks has been provided elsewhere (Swinnen

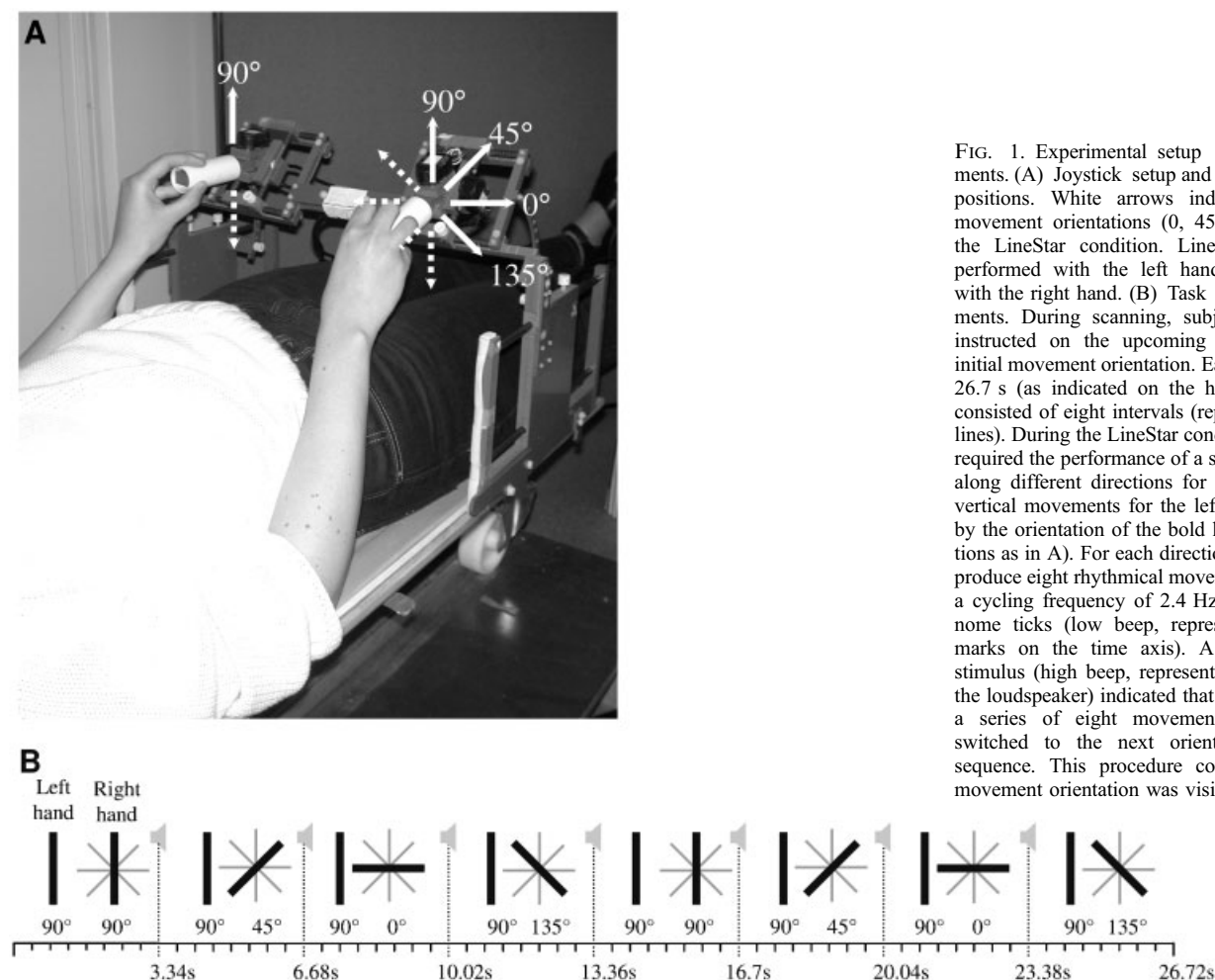


FIG. 1. Experimental setup and task requirements. (A) Joystick setup and subject's arm/wrist positions. White arrows indicate the required movement orientations ( $0^\circ$ ,  $45^\circ$ ,  $90^\circ$ ,  $135^\circ$ ) during the LineStar condition. Line movements were performed with the left hand, Star movements with the right hand. (B) Task timing and requirements. During scanning, subjects were visually instructed on the upcoming condition and the initial movement orientation. Each condition lasted 26.7 s (as indicated on the horizontal axis) and consisted of eight intervals (represented by dotted lines). During the LineStar condition, each interval required the performance of a series of movements along different directions for the right hand and vertical movements for the left hand (represented by the orientation of the bold lines, same conventions as in A). For each direction, subjects were to produce eight rhythmical movements in 3.34 s (i.e. a cycling frequency of 2.4 Hz), paced by metronome ticks (low beep, represented by the tick marks on the time axis). A different auditory stimulus (high beep, represented in the figure by the loudspeaker) indicated that subjects completed a series of eight movement cycles and had switched to the next orientation of the star sequence. This procedure continued until each movement orientation was visited twice.

*et al.*, 2001, 2002; Wenderoth *et al.*, 2003). In short, during the unimanual line drawing with the left wrist (uniLine), subjects performed rhythmical up and down movements, i.e. tracing a virtual vertical line with a required orientation angle  $\alpha_{\text{req}} = 90^\circ$  at all times. During unimanual star drawing with the right wrist (uniStar), subjects performed rhythmical movements along four different orientations with  $\alpha_{\text{req}} = 0, 45, 90$  and  $135^\circ$ . More specifically, they started with vertical up and down movements ( $\alpha_{\text{req}} = 90^\circ$ ), but switched to the subsequent orientation after eight full movement cycles (corresponding to an interval of 3.34 s) were completed and until each of the four orientations was visited twice. All movements were paced by a metronome at 2.4 Hz; in particular, switching between the different orientations during star drawing was indicated by a stressed beep, such that no additional cognitive effort arose from counting the cycles. The bimanual task required simultaneous performance of line drawing with the left wrist and star drawing with the right wrist (LineStar). Thus, subjects traced identical orientations for  $\alpha_{\text{line}} = \alpha_{\text{star}} = 90^\circ$ , but then had to maintain the line orientation ( $\alpha_{\text{line}} = 90^\circ$ ) while different star orientations were visited ( $\alpha_{\text{star}} = 45, 0, 135^\circ$ ). All movements were executed without any visual feedback. In addition to the LineStar drawing condition, subjects performed three extra bimanual tasks: (1) star-drawing left while line drawing right (StarLine), (2) line drawing left while line drawing right (LineLine) and (3) star drawing left while star drawing right (StarStar). However, these conditions were not considered in the present study, but are published in an accompanying paper (Wenderoth *et al.*, 2004a). One day before the scanning session, subjects practised for 1 h in a dummy scanner to perform the aforementioned tasks. Moreover, they were trained to fixate a cross, displayed in front of them at all times, to avoid confounding eye-movements.

### Scanning procedures

The fMRI measurements were executed on a 1.5-T MR Siemens Sonata scanner using a quadrature head coil. Each scan session began with the acquisition of a three-dimensional high-resolution T1-weighted image (MPRAGE, TR/TE = 11.4/4.4 ms, TI = 300 ms, field of view = 256 mm, matrix =  $256 \times 256 \text{ mm}^2$ , slab thickness = 160 mm, 160 slices) for anatomical details. Afterwards, subjects performed eight scanning runs, each containing 224 gradient-echo echoplanar T2-weighted functional images (TR/TE = 2840/50 ms, field of view 192 mm, matrix =  $64 \times 64 \text{ mm}^2$ , slice thickness = 4 mm, 36 sagittal slices). Each run consisted of three blocks of the following conditions: (1) uniLine, (2) uniStar, (3) LineStar, (4) StarLine, (5) LineLine, (6) StarStar and (7) rest. This paper focuses mainly on the first three movements and the rest condition, while the other bimanual movement conditions are compared in detail in an accompanying manuscript (Wenderoth *et al.*, 2004a). However, to ensure that areas responding more strongly to the bimanual than to the sum of the unimanual conditions do not solely reflect directional interference, we will also report qualitative data for the bimanual compatible StarStar condition in Fig. 5. Each condition lasted 26.7 s, corresponding to 9.4 scans. During the scan session, the upcoming condition as well as the start orientation was indicated visually by a template appearing 1.5 s prior to task initiation and remaining visible for 3 s. Conditions as well as the start orientations of the star task were randomized across runs and subjects. Between runs, there was a short break of approximately 3 min.

### Kinematic analysis

Using interactive software (Matlab 5.3), all drawing movements were divided into eight intervals, each lasting 3.34 s (i.e. the imposed time

to complete eight movement cycles along one orientation). For the uniStar and the LineStar tasks, these intervals were ordered in accordance with the orientation traced by the star drawing hand ( $\alpha_{\text{Star}} = 90, 45, 0$  and  $135^\circ$ ). For the uniLine task, the intervals were assigned to the four principal orientations of a virtual star drawing hand, even though subjects traced  $\alpha = 90^\circ$  at all times. Within each interval, the orientation angle was calculated by  $\alpha = \arctan[(y_2 - y_1)/(x_2 - x_1)]$ , with  $\alpha \in [\alpha_{\text{req}} - 90, \alpha_{\text{req}} + 90]$  and  $(x_1, y_1), (x_2, y_2)$  indicating the coordinates of two consecutive turning points. From these data, mean as well as standard deviation ( $\alpha_{\text{SD}}$ ) of  $\alpha$  were determined and the orientation error ( $\alpha_{\text{Error}}$ ) was calculated as the absolute difference between the required and the observed mean  $\alpha$ . For the statistics,  $\alpha_{\text{Error}}/\alpha_{\text{SD}}$  were subjected to a  $2 \times 2 \times 4$  analysis of variance with repeated measurements (repeated-measures ANOVA) using the within-factors MODE (unimanual vs. bimanual), TASK (Line vs. Star) and ORIENTATION of the star drawing hand (90, 45, 0, 135°). Additionally, we determined movement amplitude (i.e. the Euclidean distance between two turning points) as well as cycle duration (i.e. the temporal delay between two consecutive movement maxima and minima, respectively). These secondary movement parameters were subjected to a repeated-measures ANOVA with the factor MODE (unimanual vs. bimanual) to explore whether they represent potential confounds for activation differences between unimanual and bimanual movements. Significant main effects and interactions were further explored by Tukey *a posteriori* tests. The level of significance was set to  $\alpha = 0.05$ .

### Imaging analysis

Imaging data were analysed with the Statistical Parametric Mapping software (SPM99; <http://www.fil.ion.ucl.ac.uk/spm/>; Wellcome Department of Cognitive Neurology, London, UK) (Friston *et al.*, 1995a,b). The functional images were realigned to the first volume of each run to correct for head movements and slice timing was applied to correct for differences in acquisition time during scanning. After coregistering the functional images to the anatomical image, they were spatially normalized into a standard reference frame (Talairach & Tournoux, 1988), using a representative brain (MNI, Montreal Neurological Institute) as a template. All functional images were subsampled to a voxel size of  $2 \times 2 \times 2$  mm and smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM). For the first-level analysis, a general linear model was used, containing for each condition a delayed boxcar function convolved with the standard SPM99 hemodynamic response function. Additionally, six movement parameters derived from realignment (translation and rotation in  $x, y, z$  dimension) were added as covariates of no interest. Contrasts of interest were calculated for each subject and run individually. Subsequently, these contrasts were entered into a second-level mixed-effects analysis. Throughout we report significantly activated voxels in MNI coordinates.

### Neural network representing the coordination effort

Areas representing the higher effort of the central nervous system during the coordination of bimanual vs. unimanual movements were determined in accordance with a procedure introduced by Ramnani *et al.* (2001). First, all voxels were determined for which activation was higher during the bimanual than during the averaged unimanual tasks. Therefore, we calculated the contrast  $[\text{LineStar} - (\text{uniLine} + \text{uniStar})/2]$  that was subsequently thresholded at  $t = 3.2$  ( $P < 0.001$ , uncorrected for multiple comparisons; note that a relative liberal threshold was used to include all potentially involved voxels in the subsequent analysis). The resulting network was used as a mask and within this network we determined those areas for which the

response to the bimanual task was higher than would be expected from summing up the responses to the unimanual conditions. This was done by calculating the interaction [LineStar – uniLine – uniStar + Rest]. The statistical threshold indicating significance was set to  $t = 4.39$  ( $P < 0.05$ , corrected for multiple comparisons in the whole brain volume). The identified network represents areas reflecting the coordination effort, i.e. they were more strongly activated by the bimanual task than by summing up the activation of the unimanual subtasks.

#### Detailed analysis of frontal midline structures

Based on previous studies (Stephan *et al.*, 1999a; Swinnen, 2002; Carson & Kelso, 2004), it was hypothesized that frontal midline structures, i.e. the SMA and cingulate cortex, play a crucial role in bimanual coordination. To scrutinize mesio-frontal activity in further detail, we performed a region of interest (ROI) analysis. Therefore, we defined eight ROIs subdividing the frontal cortex of the left and right hemisphere in an anterior and posterior portion [the border was the vertical plane passing through the anterior commissure (VCA), i.e. at  $y = 0$  mm] and in a dorsal and a ventral portion [the border was the horizontal plane at  $z = 54$  mm in MNI coordinates, as suggested by previous data (Paus *et al.*, 1996)] containing mainly the precentral cortex and the cingulate cortex, respectively (see Fig. 5B). Each ROI was defined by a box of  $14 \times 20 \times 20$  mm in  $x$ ,  $y$ , and  $z$  dimension located either left or right from the midline. In accordance with Picard & Strick (1996), the antero-dorsal portion corresponds roughly to the pre-SMA, the antero-ventral portion to the posterior part of the rostral cingulate zone (RCZp), the posterior-dorsal portion to SMA-proper, and the posterior-ventral portion to the caudal cingulate zone. Activation within an ROI was considered to be significant when  $P < 0.05$ , corrected for multiple comparisons within each ROI, was reached on cluster level.

## Results

### Kinematic data

Figure 2 shows exemplary displacement data (Fig. 2A, C and E) as well as the instantaneous movement direction  $\alpha$  of the left (light gray) and right wrist (dark gray) for the unimanual line task (Fig. 2B), the unimanual star task (Fig. 2D) and the bimanual line-star task (Fig. 2F). Whereas the subject complied well with the directional requirements during unimanual task execution, directional accuracy and consistency decreased markedly when the subtasks were performed simultaneously (i.e. bimanual). In particular, when hands moved along orthogonal directions a strong mutual bias emerged, such that the left and right wrist's movement orientation differed substantially from the required  $90^\circ$  and  $0^\circ$ , respectively (Fig. 2E and F). To scrutinize unimanual vs. bimanual performance on group level, variability ( $\alpha$ SD) as well as mean orientation error ( $\alpha$ Error) of the produced movement direction for each of the four principal orientations of the star drawing were averaged between the star and line tasks. Both  $\alpha$ Error (Fig. 3A) and  $\alpha$ SD (Fig. 3B) were significantly increased when subjects performed bimanual as compared with unimanual movements ( $F_{1,9} > 10.5$ ,  $P < 0.05$  and  $F_{1,9} > 30.2$ ,  $P < 0.001$ , respectively). This marked deterioration of bimanual vs. unimanual performance became most prominent when the right hand moved along the  $\alpha = 0^\circ$  or  $\alpha = 135^\circ$  orientations (MODE  $\times$  ORIENTATION interaction for  $\alpha$ Error,  $F_{3,27} > 5.8$ ,  $P < 0.005$ ; for  $\alpha$ SD,  $F_{3,27} > 30.9$ ,  $P < 0.001$ ) and was more strongly reflected by left (line task) than by right hand movements (star task) (MODE  $\times$  TASK interaction only for  $\alpha$ SD,

$F_{1,9} > 17.2$ ,  $P < 0.005$ ). Secondary movement parameters such as movement amplitude and cycle duration did not differ significantly between uni- and bimanual movements ( $P > 0.2$ ). Taken together, performing the line and the star-drawing task together in a bimanual setting resulted in a significant decrease of directional accuracy and consistency, indicating that bimanual task performance was much more effortful than each task in isolation.

### Brain activation during unimanual and bimanual conditions vs. rest

The unimanual line drawing with the left hand activated a typical motor network containing the right SMA, right dorsal precentral gyrus, right central sulcus, right postcentral gyrus, right parietal operculum, right basal ganglia, right thalamus, left cerebellum and left inferior temporal gyrus (Fig. 4A and Table 1). The unimanual star drawing with the right hand activated left SMA, left ventral precentral gyrus, bilateral dorsal precentral gyrus, left central sulcus, left postcentral gyrus, bilateral parietal operculum, bilateral superior parietal cortex, left basal ganglia, left thalamus and right cerebellum (Fig. 4B and Table 1). Thus, the unimanual star condition activated a more bilateral network than the unimanual line drawing, which was particularly pronounced in the superior parietal cortex. This extra activation of the right hemisphere reflects the higher spatial complexity of the star as compared with the line drawing, which is further underlined by the fact that movements with the nondominant rather than the dominant hand evoke more bilateral activation (Kim *et al.*, 1993; Verstynen *et al.*, 2004). Bimanual execution of the LineStar task activated primarily a bilateral motor network containing right superior frontal gyrus, bilateral SMA, bilateral dorsal precentral gyrus, bilateral central sulcus, bilateral postcentral gyrus, bilateral parietal operculum, right superior parietal gyrus, right posterior middle temporal gyrus, right basal ganglia, bilateral thalamus and bilateral cerebellum (Fig. 4C and Table 1).

### Brain activation reflecting coordination effort

To identify the areas reflecting the coordination effort arising from bimanual actions, we determined which regions were more strongly activated during the bimanual condition as compared with the sum of the hemodynamic responses evoked by each of the unimanual subtasks. The effort arising from the control of bimanual vs. unimanual movements is highly interwoven with overcoming spatial interference. To ensure that the identified areas indeed reflect bimanuality and not predominantly spatial interference, we additionally report data of the StarStar condition (Fig. 5, white bars). This condition is of a bimanual nature, but does not evoke spatial interference effects between the limbs. Note that areas which solely respond to directional interference but not to bimanuality should not be activated in the StarStar condition. The network reflecting the coordination effort included several frontal and parietal areas and, in particular, several mesial structures (Fig. 5, Table 2). Within the lateral frontal cortex, activation was found in the right superior frontal gyrus (which tended to be bilaterally activated) (Fig. 5A, 1) extending to the right precentral gyrus and peaking close to the central sulcus (Fig. 5, 2). In contrast to the right superior frontal gyrus, which reflected mainly bimanual activity and was barely activated during the unimanual tasks, the right precentral gyrus was more strongly activated during unimanual line drawing than during unimanual star drawing (see barplot). This suggests that this precentral activation was not exclusively related to bimanual control but also contributed to

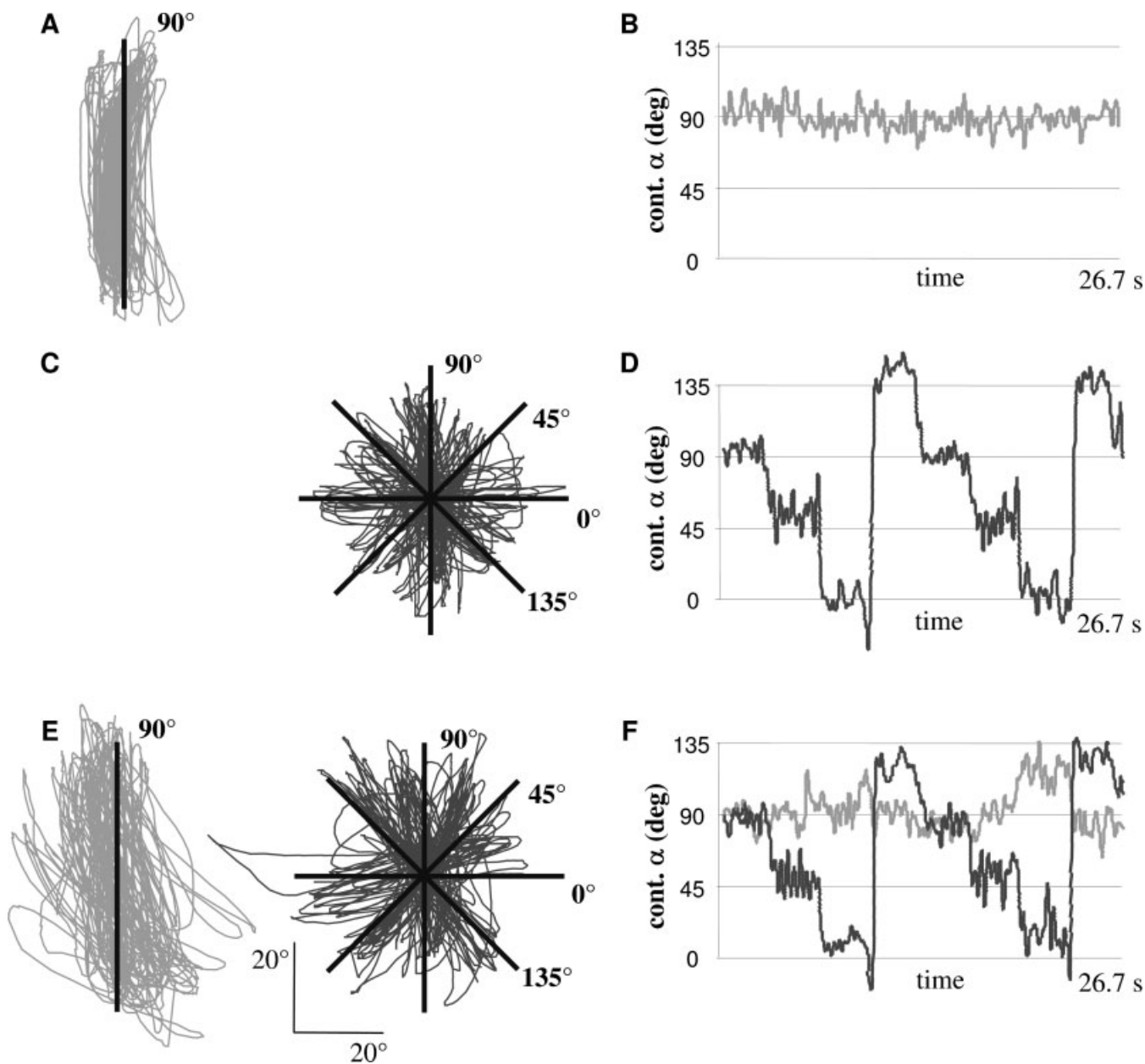


FIG. 2. Exemplary behavioral data of a typical subject. Representative examples of displacements of the left (light gray) and right (dark gray) joystick are shown for the unimanual Line (A), the unimanual Star (C), and the bimanual LineStar condition (E). For each condition, the continuous phase angles (cont.  $\alpha$ ) produced by the left (light gray) and right wrist (dark gray) are shown as a function of time (B, D and F). Note that for the unimanual conditions, the subject complied well with the required orientations, whereas during the LineStar condition, the line orientation (E, F red) deviated substantially from the required  $90^\circ$ .

unimanual movements executed with the contralateral (i.e. left) wrist. Within the parietal cortex, an increased hemodynamic response was observed bilaterally in the precuneus (Fig. 5A, 4 and 5) extending to the superior parietal gyrus (Fig. 5A, 3) as well as in the right transverse parietal sulcus (Fig. 5A, 6). These areas were increasingly activated from unimanual line to unimanual star, and particularly to the bimanual LineStar condition. Interestingly, all parietal regions responded strongly to the unimanual star drawing task that was executed with the right hand, irrespective of whether they were located in the left or the right hemisphere. This finding suggests that parietal activity was not primarily related to the control of contralateral hand movements, but also reflected higher spatial requirements during unimanual star than during unimanual line drawing.

Special attention was paid to the mesial frontal areas (Fig. 5B and C). Anterior to the VCA line, significant activation was found for a large cluster at the transition from the dorsal to the ventral portion of the left hemisphere. However, significance on cluster level was only reached for the ventral portion, which also contained the cluster's activation peak ( $x = -4$ ,  $y = 4$ ,  $z = 52$ ;  $P < 0.05$ ). This area corresponds roughly to the RCZp as defined by Picard & Strick (2001) and responded predominantly to the bimanual condition, whereas it was only moderately activated by unimanual movements (Fig. 5B). Posterior to the VCA line, the only activation was found bilaterally in the dorsal portion ( $x = -14$ ,  $y = -6$ ,  $z = 74$ ;  $x = 14$ ,  $y = -2$ ,  $z = 68$ ;  $P < 0.05$ ) corresponding to SMA-proper (Picard & Strick, 2001) that responded strongly to bimanual movements, but was



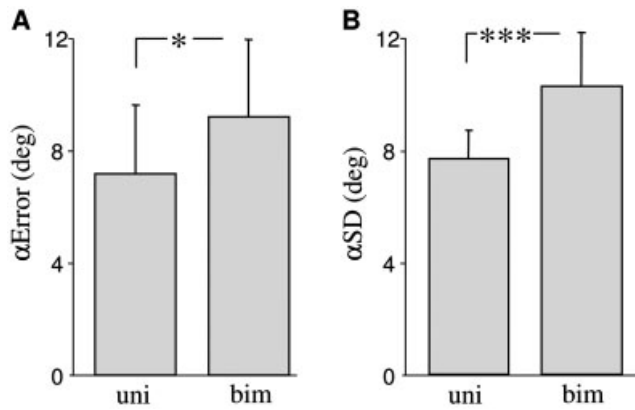


FIG. 3. Behavioral results on group level. Evidence for an increased coordination effort as indicated by directional interference during the scanning sessions. The mean orientation error ( $\alpha$ Error) (A) and orientation variability ( $\alpha$ SD) (B) are shown for the averaged unimanual (uni) and the bimanual task (bim).

also activated during the star drawing task (Fig. 5C). For other mesial ROIs, we found no evidence that the bimanual condition evoked a surplus of activity as compared with the sum of unimanual conditions.

Note that all reported right parietal and frontal areas responded also to the StarStar condition (Fig. 5, white bars), which requires bimanual movements, but does not evoke spatial interference. This confirms that the identified areas are not activated by spatial interference only, but reflect, at least partly, bimanuality.

## Discussion

In the present study, we investigated which brain areas reflect the coordination effort that emerges when the right and left limb are moved simultaneously along incompatible directions. We identified a network containing several structures within dorso-frontal and superior parietal cortex. Previous imaging studies have repeatedly shown that mesial frontal areas and, particularly, SMA plays an important role in bimanual coordination (see above). Additionally, results in patients (Stephan *et al.*, 1999a) have led to the view that the anterior cingulate cortex (ACC) might also provide an important contribution to bimanual actions (Swinnen, 2002; Carson & Kelso, 2004). However, direct experimental evidence suggesting that the ACC is activated by coordination tasks is scarce. Therefore, we performed an ROI analysis on several subdivisions of the mesial frontal cortex to further elicit the differential involvement of frontal midline structures in the control of bimanual movements. In the following paragraph we discuss the contribution of these areas to the control of coordinated behavior.

### Kinematic data

From the behavioral data, we determined movement performance by spatial parameters representing accuracy and consistency of the produced movement direction, respectively. This analysis revealed that bimanual LineStar drawing performance was substantially worse than unimanual drawing (Fig. 3), confirming that bimanual coordination was more than ‘the sum of the parts’. Moreover, bimanual performance was particularly poor when the hands had to move along

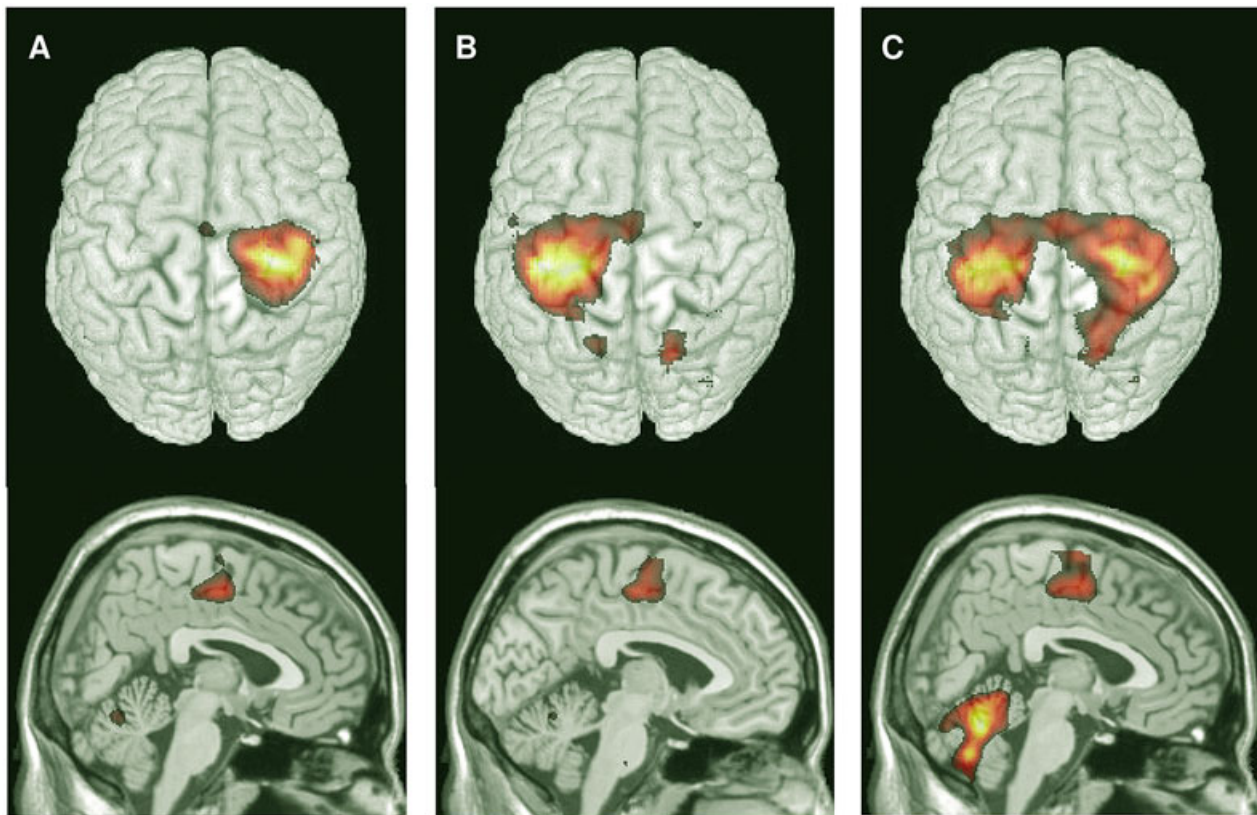


FIG. 4. Brain activation for unimanual and bimanual movement conditions vs. rest. Mesial view and rendered top view of areas significantly activated by the unimanual Line drawing with the left wrist (A), unimanual Star drawing with the right wrist (B) and bimanual LineStar drawing (C),  $P < 0.05$  corrected for multiple comparisons.

TABLE 1. Cortical areas activated by uniLine &gt; Rest, uniStar &gt; Rest, and LineStar &gt; Rest

Brain region	MNI Coordinates*								
	uniLine > Rest			uniStar > Rest			LineStar > Rest		
	x	y	z	x	y	z	x	y	z
Medial precentral gyrus (SMA proper)									
L				-2	-10	66	-2	-10	56
R	2	-8	68				4	-10	56
Anterior cingulate cortex, caudal zone									
L				-8	-18	50			
R	6	-12	50						
Lateral precentral gyrus (PMd)									
L				-24	-10	66	-26	-8	64
R	20	-16	70	28	-8	50	28	-10	62
Postcentral/precentral gyrus (SMI)									
L				-38	-26	56	-28	-28	56
R	40	-26	50				38	-30	60
Anterior inferior temporal gyrus									
L	-48	-2	-36						
R									
Parietal operculum									
L				-46	-24	18			
R	46	-24	18	58	-28	14	42	-30	18
Superior parietal gyrus									
L				-16	-62	60			
R	46	-24	18	18	-66	62	18	-62	60
Basal ganglia									
L				-28	-10	2			
R	28	-6	-2				28	-6	2
Thalamus									
L				-12	-22	6			
R	16	-20	4				14	-20	6
Anterior cerebellum, vermis									
L	-4	-62	-20				-4	-62	-20
R				6	-60	-26	2	-60	-22
Anterior cerebellum, hemispheres									
L	-16	-52	-22				-18	-52	-28
R				16	-50	-22	20	-50	-26
Posterior cerebellum, vermis									
L	4	-66	-38				-4	-66	-38
R				6	-66	-38	2	-68	40
Posterior cerebellum, hemispheres									
L	-18	-58	-54				-20	-58	-54
R				20	-52	-56	-18	-56	-54

\*Voxel locations for areas significantly activated by at least one of the three movement conditions ( $P < 0.05$  corrected for multiple comparisons with an extend larger than 50 voxels). Voxels are reported in MNI coordinates.

orthogonal directions, i.e. when the left and right hand movement direction were highly incompatible. By contrast, secondary movement parameters, such as amplitude or cycle duration, did not differ significantly between conditions. Accordingly, brain activation differences, as revealed by comparing the bimanual blood oxygenation level-dependent (BOLD) response to the sum of the unimanual responses, can be interpreted as reflecting the coordination effort required for integrating the spatial features of bimanual movements.

### Imaging data

We aimed to identify the regions representing the coordination effort, i.e. areas which were more activated in the bimanual task than would be expected by summing up the activations of the unimanual subtasks. Comparing bimanual vs. unimanual movements, a primarily right-hemispheric superior parietal – dorsofrontal network was activated,

representing the putative neural correlates of the coordination effort arising from spatial integration of the limbs.

### Limitations of the statistical approach and potential confounds relating to coordination, interference and complexity

The bar plots of Fig. 5 indicate that, particularly for the line drawing task, some areas exhibited a deactivation relative to the rest condition. This might result from the fact that some areas were shown to remain active during rest but became deactivated for simple tasks (Raichle *et al.*, 2001; Mazoyer *et al.*, 2001; Greicius *et al.*, 2003). Previous studies found that this 'default mode of brain functioning' in rest is represented by the ventral anterior and the posterior cingulate, whereby the activity of the latter often extended to the neighboring precuneus. Even though the precuneus activation yielded in our study is not adjacent to the cingulate cortex, we cannot exclude that it remained active during the rest as compared with the single limb conditions. Therefore, it is possible that the coordination effort contrast, which was calculated relative to the rest condition, underestimated the unimanual task activation. However, there are also other likely mechanisms causing deactivation such as the reallocation of blood resources to strongly activated neighboring areas (Harel *et al.*, 2002) or, more importantly, the neural inhibition of areas not involved in the required motor task (Kudo *et al.*, 2004; Stefanovic *et al.*, 2004). Even though we cannot distinguish which of the above mechanisms caused the underactivation of the unimanual task, it is important to stress that the identified coordination effort network was more strongly activated for the bimanual than for the unimanual tasks, making the involved areas the appropriate candidates to reflect coordination demands.

Our analysis of the coordination effort assumes that specific coordination areas exhibit additive response properties when two tasks are executed in parallel. Although many earlier studies used a similar approach, this logic fails to identify areas which are highly involved in coordination, but exhibit some form of 'under-additivity' (i.e. regions in which the sum of subtask activity is smaller than or equal to the bimanual task). Such under-additivity might be found, for example, within the primary motor areas, which may already be highly activated during the single limb tasks such that ceiling effects prevent the doubling of the BOLD response. Moreover, it can be assumed that some aspects of the bimanual task are represented as an integrated entity such that a common movement plan is generated for both hands. In an additional analysis, we determined which areas exhibited pronounced under-additivity (see Appendix). We identified a region in the parietal operculum which was previously shown to contribute to multisensory processing of auditory and somatosensory information. No other areas reached significance. This finding suggests that the bimanual task was probably executed in accordance with a common temporal plan. In the following sections we focus on areas reflecting the coordination effort.

It is important to bear in mind that the coordination effort is strongly tied to other covarying factors, such as overcoming directional interference or increases of movement complexity in general. However, both covarying aspects are intrinsic to a bimanual interference task, such that no comparable single-limb control conditions exist. Thus, based on the present results alone, we cannot disentangle whether the activated areas reflect predominantly the coordination effort arising from moving two limbs in parallel vs. only one limb, or directional interference and movement complexity, respectively, arising as a consequence of moving both arms simultaneously along incompatible vs. compatible directions. Therefore, we discuss our

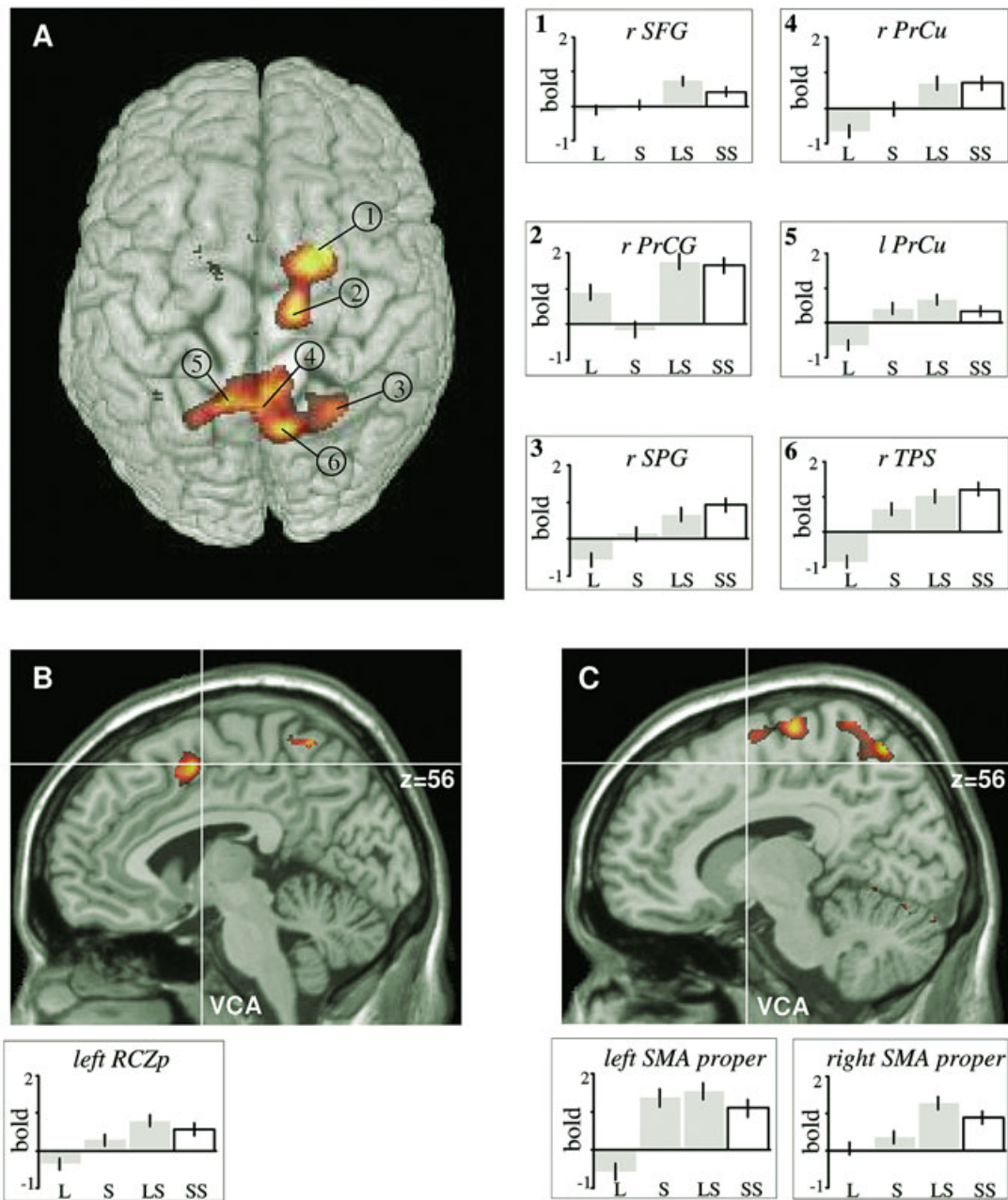


FIG. 5. Coordination effort as revealed by comparing the bimanual and the sum of the unimanual activations. (A) Areas reflecting the coordination effort ( $P < 0.05$ , corrected for multiple comparisons). For significant activation maxima, bar plots show the estimated blood oxygenation level-dependent (BOLD) response for the unimanual Line drawing (L), the unimanual Star drawing (S) and the bimanual LineStar drawing (LS) condition. The BOLD response is shown in arbitrary units. Midline activation displayed on top of a mesial view of (B) the left hemisphere ( $x = -4$  mm) and (C) the right hemisphere ( $x = 10$  mm). The VCA line delineating the border between the anterior and the posterior portion is marked with a vertical line, and the border between the dorsal and the ventral portion at  $z = 54$  is marked with a horizontal line. Bar plots show the estimated BOLD response for significantly activated ROIs ( $P < 0.05$  on cluster level, corrected for multiple comparisons within each ROI). 1. SFG: superior frontal gyrus, 2. PrCG: precentral gyrus, 3. SPG: superior parietal gyrus, 4/5. PrCu: precuneus, 6. TPS: transverse parietal sulcus, RCZp: posterior part of the rostral cingulate zone, roughly located in the anterior-ventral portion, SMA-proper: posterior part of the supplementary motor area, roughly located in the posterior-dorsal portion of the frontal midline region (numbering in accordance with Table 1).

present findings in light of earlier results addressing specifically the neural correlates of directional interference (Wenderoth *et al.*, 2004a), movement complexity (Deiber *et al.*, 1996; Sadato *et al.*, 1996; Catalan *et al.*, 1998; Haslinger *et al.*, 2002; Debaere *et al.*, 2004; Haaland *et al.*, 2004) and bimanuality (Koeneke *et al.*, 2004). In particular, we rely on findings of an accompanying paper in which the brain areas specifically reflecting directional interference were investigated in the same subjects, but by comparing only bimanual conditions (Wenderoth *et al.*, 2004a). [Note that this accompanying

study compared only bimanual conditions, such that the observed activation differences do not reflect bimanual vs. unimanual demands.]

All areas identified by the bimanual vs. unimanual contrast reflect the coordination effort. However, some areas such as the lateral parieto-frontal areas, i.e. superior parietal gyrus (Fig. 5A-4), the precentral gyrus (Fig. 5A-2) and the superior frontal gyrus (Fig. 5A-3), as well as SMA-proper (Fig. 5C) were previously shown to reflect also directional interference (Wenderoth *et al.*, 2004a) as well as movement complexity (Deiber *et al.*, 1996; Sadato *et al.*, 1996; Catalan *et al.*,



TABLE 2. Cortical areas reflecting the coordination effort

Brain region	Fig. 5A reference number	MNI coordinates			<i>t</i> -value
		<i>x</i>	<i>y</i>	<i>z</i>	
Right superior frontal gyrus	1	20	-2	64	5.81
Left superior frontal gyrus*	-	-20	4	68	3.37
Right precentral gyrus	2	14	-22	72	5.51
Right superior parietal gyrus	3	30	-56	62	5.11
Left superior parietal gyrus*	-	-36	-50	58	3.40
Right dorso-anterior precuneus	4	4	-50	70	5.19
Left dorso-anterior precuneus	5	-10	-52	68	5.60
Right transverse parietal sulcus	6	10	-64	60	5.59

Voxel locations and *t*-values for areas reflecting the coordination effort ( $P < 0.05$  corrected for multiple comparisons). \*Areas showing a trend to bilateral activation ( $P < 0.001$ , uncorrected). Numbering is used in accordance with Fig. 5A. Significant activation peaks are reported in MNI coordinates.

1998; Harrington *et al.*, 2000; Haslinger *et al.*, 2002; Debaere *et al.*, 2004; Haaland *et al.*, 2004). Thus, we cannot be sure that these areas represent predominantly the bimanual nature of the task. By contrast, frontal and parietal midline structures, i.e. the ACC and the precuneus, were specifically activated by the coordination effort contrast, whereas they did not reach significance for the directional interference comparison. This difference suggests that both areas respond mainly to bimanuality and to a lesser degree to spatial interference. This is further confirmed by the result that both midline areas are considerably activated during the bimanual StarStar condition in which interference is presumably absent. Moreover, neither activity of the ACC nor of the dorso-anterior precuneus appears to depend on motor complexity *per se*, as suggested by unimanual studies (Harrington *et al.*, 2000; Deiber *et al.*, 1996; Sadato *et al.*, 1996; Catalan *et al.*, 1998; Haslinger *et al.*, 2002; Haaland *et al.*, 2004) and, more importantly, one bimanual study manipulating complexity (Debaere *et al.*, 2004). Note, however, that some unimanual sequencing studies identified complexity-related activation changes within a portion of the precuneus which was located more ventro-posteriorly ( $> 25$  mm, see also discussion below) (Deiber *et al.*, 1996; Sadato *et al.*, 1996; Haslinger *et al.*, 2002).

Finally, recent research suggests that a similar network, as activated during bimanual coordination, also emerges during within-hand interfinger coordination (Ehrsson *et al.*, 2002; Koenke *et al.*, 2004). Therefore, our bimanual paradigm serves mainly as one example of interlimb coordination in general while the question of which areas respond mainly to bimanuality as compared with coordination requirements in general remains unresolved.

In summary, coordination effort, spatial interference and motor complexity are intrinsic to interlimb coordination. However, in light of previous imaging studies, we consider the identified mesial/paramesial areas to play a major role in the spatial integration of bimanual vs. unimanual movements. In the following sections we discuss their specific contribution to bimanual actions in particular as well as to the control of voluntary movements in general.

### Anterior cingulate cortex

As compared with unimanual movements, bimanual movements led to a strong activation of the RCZp as defined by Picard & Strick (2001), which has been linked with manual actions (Paus *et al.*, 1993). The RCZp is part of the ACC, which becomes generally activated when task difficulty is high (Paus *et al.*, 1998; Bush *et al.*, 2000; Hopfinger *et al.*, 2001). This might reflect an increase of arousal (Paus *et al.*, 1998;

Sturm *et al.*, 1999) but also higher demands to direct attention to task-relevant events (Weissman *et al.*, 2003, 2005; Thiel *et al.*, 2004). Thus, the ACC appears to play an important role in conflict monitoring (Carter *et al.*, 1998; Botvinick *et al.*, 1999). More specifically, it has been hypothesized that the ACC detects a conflict and signals, via connections to the lateral prefrontal cortex (LPFC), that more cognitive control is needed (Kerns *et al.*, 2004). As locus of the central executive, the LPFC then becomes activated to comply with the higher cognitive demands. Interestingly, we observed activation not only in the ACC but also in a small but highly significant spot in the LPFC (1 voxel at  $x = -40$ ,  $y = 34$ ,  $z = 32$ ,  $P < 0.05$  corrected), located in a similar region identified in earlier conflict studies (MacDonald *et al.*, 2000; Garavan *et al.*, 2002). Thus, the increased activity of the ACC observed in our study might indicate that bimanual as compared with unimanual movements were more difficult and required a higher level of cognitive control, presumably to direct attention between tasks or to monitor potential conflicts. Accordingly, both the interfering LineStar but also the noninterfering StarStar condition led to a higher activation of the ACC than the unimanual movements. Furthermore, ACC activity was somewhat higher for the LineStar than for the StarStar condition, indicating that the ACC activation is additionally modulated by interference. More specifically, increased cognitive control is mandatory when habitual behavior needs to be blocked to allow the execution of less familiar actions, as was the case in our experiment. Bimanual coordination research has shown that mirror-symmetric movements represent an intrinsically preferred coordination mode, which refers to a sort of 'default coupling' between the limbs (for an overview see Kelso, 1995; Swinnen, 2002; Swinnen & Wenderoth, 2004). Accordingly, the natural tendency to move the arms in mirror-symmetry has to be inhibited to allow simultaneous movements along different directions. In this context, it is hypothesized that the RCZp, which is involved in response selection (Picard & Strick, 2001), funnels cognitive commands to motor structures such that appropriate responses are facilitated while unwanted actions are suppressed (Paus *et al.*, 1993; Bush *et al.*, 2000). The RCZp has dense connections to the primary motor cortex (M1) as well as to the SMA (Morecraft & Van Hoesen, 1992; Wang *et al.*, 2001), which are both heavily activated during bimanual movements (for an overview see Swinnen & Wenderoth, 2004; Wenderoth *et al.*, 2004b).

In addition to many other functions, the SMA-proper also appears to be involved in the control of interhemispheric information interchange (Serrien *et al.*, 2002). In particular, disrupting SMA-proper activity during nonsymmetric bimanual movements (e.g. antiphase) results in an involuntary switch to the symmetric coordination mode, as shown by inducing 'virtual lesions' with transcranial magnetic stimulation (TMS) (Meyer-Lindenberg *et al.*, 2002; Obhi *et al.*, 2002; Serrien *et al.*, 2002; Steyvers *et al.*, 2003). Based on these findings as well as the anatomical connections between the ACC and SMA, it is tempting to speculate that the ACC has a modulatory influence on SMA activity in order to suppress the intrinsically favored coordination tendencies (i.e. mirror-symmetric movements) and to facilitate less familiar bimanual movements (i.e. movements along incompatible directions or different trajectories). This hypothesis is supported by lesion studies showing that patients with a damaged ACC are unable to perform nonsymmetrical bimanual movements, while symmetrical actions are not impaired (Stephan *et al.*, 1999a). This observation is in good agreement with the finding that lesions to the dorsal ACC can result in a general impairment of response inhibition (Swick & Turken, 2002). In summary, our data suggest that SMA-proper is probably involved in the control of interhemispheric information flow, which forms a key function in bimanual control. The ACC, by contrast, appears to play a more generic role related to

cognitive control and response inhibition that extends beyond bimanual coordination.

### *Precuneus and the adjacent paramesial area*

We found high activation within bilateral dorso-anterior precuneus. Activation was more pronounced in the right hemisphere, extending to a paramesial region around the transverse parietal sulcus. Traditionally, the precuneus has been associated with memory retrieval (Buckner *et al.*, 1996; Smith & Jonides, 1997; Krause *et al.*, 1999; Schmidt *et al.*, 2002; Shannon & Buckner, 2004), becoming additionally activated when imagery is used as a mnemonic strategy (Shallice *et al.*, 1994; Fletcher *et al.*, 1995, 1996; Halsband *et al.*, 1998). During motor tasks, this region was found to be activated during sequencing experiments and modulated its activity as a function of sequence complexity and length, respectively. However, these more (motor-) memory-related studies identified consistently a ventro-posterior part of the precuneus, whereas in our study, bimanual vs. unimanual movements activated a dorso-anterior section (> 25 mm away, immediately posterior to the ascending band of the cingulate gyrus). This latter section of the precuneus is often activated during the execution or imagination of spatially demanding tasks (Grafton *et al.*, 1992; Connolly *et al.*, 2000; Astafiev *et al.*, 2003; Vanlierde *et al.*, 2003) and, in particular, when two limbs (i.e. bimanual or bipedal movements) have to be coordinated in accordance with a complex spatiotemporal pattern (Christensen *et al.*, 2000; Malouin *et al.*, 2003; Meister *et al.*, 2004).

However, it is unlikely that the mesial and paramesial areas of the parietal cortex are motor by nature, because the superior parietal cortex of the right hemisphere is considered a higher-order area that is generally involved in controlling spatial aspects of behavior. Instead, recent evidence suggests that the precuneus is involved in directing attention in space during the execution of goal-directed movements but also in the absence of overt motor responses such as attentive tracking (Culham *et al.*, 1998, 2001). Adjoining regions of the superior parietal cortex are part of a network that is activated during the shift of attention to different locations in space (Gitelman *et al.*, 1999; Beauchamp *et al.*, 2001; Vandenberghe *et al.*, 2001; Yantis *et al.*, 2002). More specifically, one spot near (< 7 mm) the area around the transverse parietal sulcus that was found in our study was previously shown to be transiently activated during a spatial shift of attention (Yantis *et al.*, 2002).

In light of these findings, we assume that the increasing activation of parietal midline structures from unimanual Line drawing to unimanual Star drawing and particularly to bimanual LineStar drawing arose from increasing demands to direct spatial attention during task execution. More specifically, during Line drawing, subjects had to attend only to one orientation in allocentric space, whereas during star drawing, they had to systematically shift attention to different orientations. This attentional shift to different allocentric orientations was also required during the bimanual LineStar drawing, on top of the division of attention between the left and right wrist. These between-effector attention shifts were probably crucial to monitor whether both limbs moved in accordance to the spatiotemporal relationships required by the bimanual task. Moreover, subjects had to imagine which orientation had to be traced, as they did not receive any external guidance via online visual feedback or a template indicating the required orientation. This could have led to an additional increase of precuneus activity, which was shown earlier to respond to spatially complex imagery tasks (Christensen *et al.*, 2000; Ogiso *et al.*, 2000; Malouin *et al.*, 2003; Vanlierde *et al.*, 2003; Meister *et al.*, 2004). Mesial parietal activity, which was significantly increased for the

bimanual as compared with the unimanual conditions, might have arisen from higher demands to direct attention in space. This effect was presumably amplified by the requirement to imagine the to-be-traced orientation.

### Conclusion

Our study revealed for the first time direct experimental evidence that the execution of spatially complex bimanual coordination as compared with unimanual tasks activates the ACC (posterior part) as well as the dorso-anterior precuneus (posterior to the vertical band of the cingulate sulcus). The anterior cingulate is assumed to be involved in cognitive control such as directing attention to task-relevant events. During nonsymmetric bimanual movements, it may additionally exert its modulatory effect on other motor areas, such as the primary motor cortex and SMA, in order to suppress intrinsically favored mirror-movements. This suppression enables simultaneous left and right limb movements along incompatible or nonpreferred trajectories. Increased activity of the precuneus is likely associated with frequent shifts of attention between both limbs, to monitor their unique trajectories. Thus, the coordination effort emerging during bimanual actions, which is considered a prototype of a coordination task, is reflected by regions contributing to higher order functions that form an interface between cognition and action.

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### Abbreviations

$\alpha$ , orientation of the produced line drawing;  $\alpha$ Error, absolute error of  $\alpha$ ;  $\alpha$ SD, standard deviation of  $\alpha$ ; ACC, anterior cingulate cortex; BOLD, blood oxygenation level dependent; fMRI, functional magnetic resonance imaging; LineStar, bimanual line drawing with the left while star drawing with the right wrist; LPFC, lateral prefrontal cortex; MNI, Montreal Neurological Institute; RCZp, posterior part of the rostral cingulate zone; ROI, region of interest; SMA, supplementary motor area; StarStar, bimanual star drawing with both hands; TMS, transcranial magnetic stimulation; uniLine, unimanual line drawing with the left wrist; uniStar, unimanual star drawing with the right wrist; VCA, vertical plane passing through the anterior commissure.

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## Appendix

### Alternative comparisons between bimanual and unimanual movements

We compared bimanual vs. the sum of the unimanual movements to identify which areas represent the coordination effort arising from producing different movements in parallel. This approach has been frequently applied to explore the neural correlate of bimanual movements. However, other comparisons of bimanual vs. unimanual movements might provide complementary information. In particular, the inverse contrast (i.e. uniLine + uniStar – LineStar – Rest) can be used to estimate areas exhibiting some ‘under-additivity’ of the unimanual conditions. In the present study, we identified such areas within a network that was significantly activated by the bimanual and at least one of the unimanual conditions ( $P < 0.001$ , uncorrected). Significant under-additivity was found bilaterally around the parietal operculum (40, –32, 20,  $t = 7.56$ ; –46, –26, 16,  $t = 7.16$ ;  $P < 0.05$  after correction for multiple comparisons in the whole brain volume; extent threshold = 50 voxels). In addition, the comparison between the sum of the unimanual conditions and the StarStar condition revealed only the parietal operculum region of the left and right hemisphere. This area has been shown previously to contribute to multisensory processing of auditory and somatosensory information (Foxe *et al.*, 2002). In the context of our present task, it is most likely involved in timing aspects. This may indicate that the movements were executed in accordance with one common temporal plan.