

Brain Areas Involved in Interlimb Coordination: A Distributed Network

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Whereas behavioral studies have made significant contributions toward the identification of the principles governing the coordination of limb movements, little is known about the role of higher brain areas that are involved in interlimb coordination. Functional magnetic resonance imaging (fMRI) was used to reveal the brain areas activated during the cyclical coordination of ipsilateral wrist and foot movements. Six normal subjects performed five different tasks that were presented in a random order, i.e., isolated flexion-extension movements of the right wrist (WRIST) and right foot (FOOT), cyclical coordination of wrist and foot according to the isodirectional (ISODIR) and nonisodirectional (NON-ISODIR) mode, and rest (REST). All movements were auditory paced at 66 beats/min. During the coordination of both limb segments, a distributed network was identified showing activation levels in the supplementary motor area (SMA), cingulate motor cortex (CMC), premotor cortex (PMC), primary sensorimotor cortex (M1/S1), and cerebellum that exceeded the sum of the activations observed during the isolated limb movements. In addition, coordination of the limb movements in different directions was associated with extra activation of the SMA as compared to movements in the same direction. It is therefore concluded that the SMA is substantially involved in the coordination of the nonhomologous limbs as part of a distributed motor network. Accordingly, the long-standing exclusive association that has been made between this medial frontal area and bimanual (homologous) coordination needs to be abandoned and extended towards other forms of interlimb coordination (nonhomologous). © 2001 Academic Press

Key Words: interlimb coordination; fMRI; ipsilateral; kinematics; motor network; supplementary motor area (SMA).

INTRODUCTION

Even though considerable progress has been made with respect to the neural control of movement, it still remains largely unresolved which higher brain areas

are critically involved in the successful coordination of limb movements. The supplementary motor area (SMA) has generally been thought to play a leading role in the coordination of the homologous limbs, as SMA lesions have shown to disrupt bimanual movements in human as well as in subhuman primates (Laplaine *et al.*, 1977; Chan and Ross, 1988; Brinkman, 1981, 1984). In addition, imaging studies have shown strong activations in this frontal midline area during bimanual finger movements (Sadato *et al.*, 1997; Stephan *et al.*, 1999a; Jäncke *et al.*, 2000), thereby further underscoring its importance in this type of movements. Recently, however, the presumed “specific” role of the SMA in bimanually coupled movements has been debated (Donchin *et al.*, 1998; Kazenikov *et al.*, 1998, 1999; Stephan *et al.*, 1999b; Wiesendanger *et al.*, 1994).

The neuroanatomical background of nonhomologous limb coordination has not yet been addressed with the current imaging techniques. Therefore, the present study used fMRI to identify the principal brain areas involved in the coordination of the ipsilateral limbs. Comparisons were made between activations during the isolated movements of wrist and foot segments (WRIST or FOOT) and their coordination whereby the limbs moved in either the same (isodirectional, ISODIR) or in opposite directions (nonisodirectional, NON-ISODIR). Previous behavioral work has revealed that these two coordination modes are not equally difficult. Whereas movements of the limb segments in the same direction in extrinsic space can be accomplished easily in normal and pathological groups without much effort, the synchronization of the limb motions in opposite directions is more difficult and is characterized by a lower degree of accuracy and stability (Baldissera *et al.*, 1982, 1991, 1994; Kelso and Jeka, 1992; Serrien and Swinnen, 1997; Swinnen *et al.*, 1995, 1997a, 1997b). This effect is robust, as it has been demonstrated across a variety of effector combinations (e.g., wrist and ankle, forearm and lower leg).

Whereas the requirement to coordinate the limb segments is abundant in everyday activities and in recre-

ational and industrial environments, very little is known about the neural basis of coordination in humans. The latter is also of critical importance for understanding motor disorders because coordination is a dominant deficit in patients suffering from brain insults (cerebrovascular accidents) and neurodegenerative diseases (Parkinson's Disease and Huntington's Disease). Therefore, the primary question of the present study was to identify the brain areas involved in the coordination of the ipsilateral limbs and to reveal whether the process of interlimb synchronization imposes an additional load on the central nervous system, as compared to the isolated movements of the limb segments. In addition, comparisons were made between the isodirectional and nonisodirectional coordination mode to address whether their differential kinematic stability was associated with differences in the spatial distribution and degree of brain activation. More specifically, it was of primary interest to discover whether brain activation levels during coordination of the limb segments exceeded the sum of the activation levels obtained under isolated performance conditions or whether coordination required the recruitment of new brain areas that are uniquely involved in the orchestration of coordination patterns. In view of the previously described lower degree of accuracy/stability for performing the non-isodirectional as compared to the isodirectional coordination mode, higher activation levels were predicted to occur during the former as compared to the latter mode.

MATERIALS AND METHODS

Subjects. Six healthy, right-handed volunteers (three females and three males; mean age 23.5 years, range 21–28 years) without a history of neurological or psychiatric disease participated in the study. The study was approved by the local ethical committee and all subjects provided written informed consent.

Experimental design. The task consisted of cyclical flexion-extension movements of the right wrist (WRIST) or right ankle (FOOT), the cyclical coordination of the wrist and foot according to the isodirectional (ISODIR) and nonisodirectional (NON-ISODIR) mode and rest (REST). During the ISODIR coordination mode, both limb segments were either moving up or down simultaneously, whereas during the NON-ISODIR coordination mode, one limb was moving upwards whereas the other was moving downwards, or vice versa. All movements were paced by an electronic metronome (KORG DTM-12) at 66 beats per minute (one beat per complete cycle).

A cushion supported the legs to ensure a comfortable position and to allow differentiated movements of the distal segment. The right arm was extended along the trunk and the proximal part of the arm was supported to enable free movements of the wrist. The wrist and

foot were positioned in a wrist-hand and an ankle-foot orthosis, respectively, which were constructed of non-ferromagnetic materials. Movement was restricted to the sagittal plane. The frictionless axis of the orthosis was aligned with the anatomical axis of the joint such that movements were not hindered. Angular displacements of the joints were registered by means of non-ferromagnetic high precision shaft encoders (HP, 2048 pulses per revolution) fixed to the movement axis of the orthosis. To our knowledge, this is the first time that such accurate on-line kinematic recordings have been made in the fMRI environment. Movements were limited to the wrist and ankle, while the other segments were kept still. A bite-bar was used to minimise head motion. Prior to the experimental session, a 10-min practice session was held to ensure correct performance.

During a two-hour experimental scanning session, the five different conditions were presented in a random order, each for a duration of 42 s. Eight sequences, each consisting of two blocks of five randomized conditions were administered. Between the eight sequences, a rest period of three minutes was provided. The MRI images were acquired in a 1.5-T MR scanner (Siemens Vision, Erlangen, Germany), using a quadrature head coil. Each scanning session began with the acquisition of a 3-D high-resolution T1-weighted image (MPRAGE) for anatomical detail with the following parameters: 256-mm field-of-view, 1.25-mm slice thickness, 128 slices, and 256×256 in-plane matrix size. On the basis of these images, the position of the slices used for functional imaging was selected. Whole brain fMRI data with BOLD contrast were acquired using an echo-planar-gradient echo sequence with an echo time of 40 ms. Thirty-two slices were taken with a thickness of 4 mm and an interslice gap of 1 mm, 200-mm field-of-view, and 64×64 matrix size, resulting in a voxel size of $3 \times 3 \times 5$ mm. Each functional time series consisted of 125 scans (32 slices per scan), acquired every 3.5 s, resulting in a total acquisition time of 7 min, 18 s per functional time series. The first 5 scans were deleted to correct for early magnetisation effects.

Data analyses. Kinematic analysis focussed on the spatiotemporal features of the limb motions by means of cycle duration and amplitude measures. The coordination between the limb segments was assessed by means of a relative phase measure, i.e., the subtraction of the phase angles of each limb segment according to the following formula: $\Phi = \theta_w - \theta_f = \tan^{-1}[(dX_w/dt)/X_w] - \tan^{-1}[(dX_f/dt)/X_f]$, whereby w and f denotes wrist and foot, respectively. θ_w refers to the phase of the right wrist movement at each sample, X_w is the position of the right wrist after rescaling to the interval $[-1, 1]$ for each cycle of oscillation, and dX_w/dt is the normalized instantaneous velocity. The SD scores were used as a measure of relative phase consistency. In addition to

relative phase measures, temporal and spatial parameters of the right hand and right foot motions were quantified, i.e., cycle duration and amplitude. Cycle duration was defined as the time that elapsed between successive peak extension positions. The average cycle duration was computed across the 42 s trial; within-trial standard deviations were computed to assess temporal variability. The spatial measure consisted of the absolute value of the peak-to-peak amplitude for each individual cycle. This measure was averaged across each trial and the within-trial standard deviation was computed to estimate spatial variability.

fMRI image analysis was performed off-line using SPM 96 software (Wellcome Department of Cognitive Neurology, London, UK). First, all EPI images of each time series were realigned to the first functional image of the first time series to remove residual head movements. Next, the functional images were reoriented and resized (to $2 \times 2 \times 2$ -mm voxel size for single subject analysis and to $3 \times 3 \times 3$ mm for the group analysis) into the standard anatomic space defined by the MNI template as implemented in SPM 96. Images were then spatially smoothed with a Gaussian Kernel of 4 mm and 6 mm full width at half maximum for single subject and group analysis, respectively. Next, statistical parametric maps were calculated (Friston *et al.*, 1994, 1995) using a delayed boxcar to model the hemodynamic responses. These maps were thresholded at $Z > 4.75$ (corresponding to $P < 0.05$, corrected for multiple comparisons) and $P < 0.05$ for the spatial extent of the activation foci. The group analysis consisted of a conjunction analysis and fixed effects model (see Friston *et al.*, 1999a, 1999b; Price *et al.*, 1997). This enabled us to make valid inferences about the specific activations observed in our group of subjects. With this approach activations that are common to all subjects for each specified contrast are tested, which may reflect aspects of the functional anatomy that are typical for the population (i.e., normal, healthy subjects) from which the group was sampled (Friston, 1999a, 1999b).

First, all individual tasks were contrasted with the REST condition, revealing the brain regions that were involved in each of them. Second, the extra or newly activated regions resulting from coordination according to the ISODIR or NONISODIR mode were identified using the contrasts ISODIR or NONISODIR versus WRIST + FOOT. Third, the NONISODIR mode was directly compared with the ISODIR mode, to reveal potential differences in brain activation between both differentially stable coordination patterns. Finally, a more detailed comparison of the ISODIR and NONISODIR mode was explored. Since there was a clear hypothesis about the localization of the differential response to the two coordination modes, two additional techniques were used to focus and restrict the

analysis to a specific group of regions, as discussed next.

The conjunction analysis visualizes those regions that are commonly and equally activated in both contrasts, by excluding all voxels showing a significant interaction between these contrasts (threshold for conjunction $P < 0.05$). The conjunction analysis was performed between the contrasts (NONISODIR – ISODIR) and (WRIST + FOOT) – REST, revealing those regions that are part of the general network of wrist and foot movement and that respond differently to the coordination modes. Additionally region of interest (ROI) analysis (Worsley *et al.*, 1996) for the contrast NONISODIR – ISODIR was performed on the anatomically defined supplementary motor area (SMA). This frontomesial area has shown to be differentially involved for the two coordination modes during bimanual coordination (Sadato *et al.*, 1997; Stephan *et al.*, 1999b). As such, we wanted to investigate if this also pertains to the coordination of the ipsilateral limb segments. The corrected height threshold for the ROI analysis was maintained at $P < 0.05$.

RESULTS

Kinematic Data

The present kinematic data were successfully recorded on-line during the fMRI scanning sessions. In agreement with previous behavioral studies, the isodirectional mode was performed significantly more accurately and consistently (Mean absolute error of required relative phase (M) $M = 22.04^\circ$, $SD = 18.47^\circ$) than the nonisodirectional mode ($M = 27.72^\circ$, $SD = 26.42^\circ$) ($P < 0.05$ for M and $P < 0.01$ for SD), as inferred from the relative phase measures. This implies that movements occurring in the same direction were synchronized more accurately and consistently than movements in different directions.

An example of the registered angular displacements for wrist and foot and their relative phasing during isodirectional (A) and nonisodirectional (B) coordination is shown in Fig. 1. Both patterns were performed successfully. When comparing the relative phase data in A and B, it is noticed that the isodirectional coordination mode is produced more consistently (smaller range of relative phase) and more accurately (closer to the target relative phase) than the nonisodirectional coordination mode.

Amplitude measurements showed no significant differences in mean amplitude among the different experimental conditions ($P > 0.05$). Mean amplitudes of the wrist and foot were also not significantly different from each other ($P > 0.05$). A significant difference across conditions was observed for SD amplitude ($P < 0.01$). A *posteriori* tests revealed that the amplitude SD was

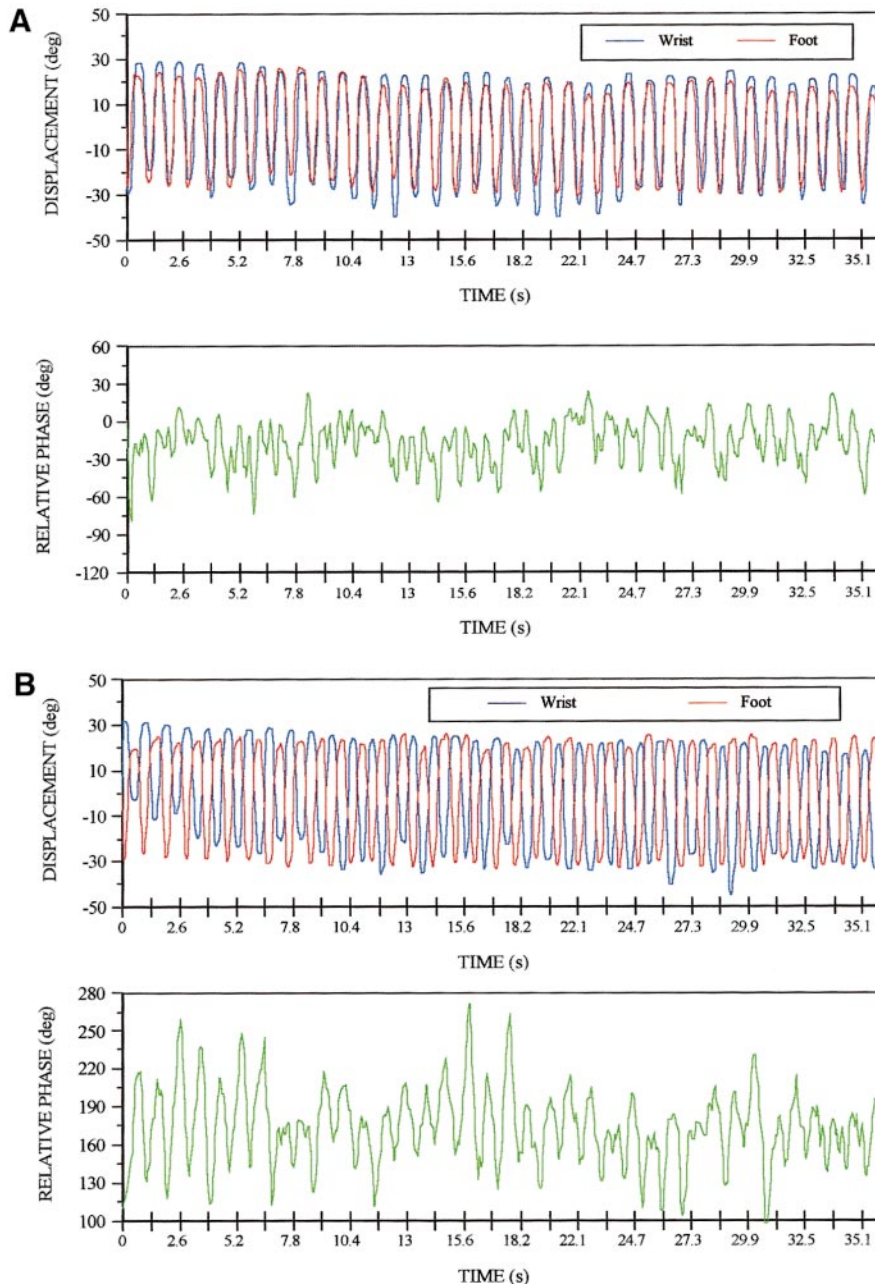


FIG. 1. Displacements of the limbs and relative phase data of representative examples of the ipsilateral coordination modes. (A) Represents a trial of the isodirectional pattern, (B) represents a trial of the nonisodirectional pattern.

significantly lower for movements of single limbs ($SD = 2.41^\circ$) than for the nonisodirectional mode ($SD = 2.93^\circ$) ($P < 0.05$), and for the isodirectional ($SD = 2.36^\circ$) as compared to the nonisodirectional mode ($P < 0.01$).

All conditions were paced by a metronome, beating at 1.1 Hz. No significant differences among conditions were identified for mean cycle duration ($P > 0.05$), whereas the SD scores differed ($P < 0.01$). Mean and SD scores for isolated limb movements, and isodirectional and nonisodirectional movements were 888 ms

(47.7 ms), 896 ms (46.7 ms), 897 ms (61.8 ms), respectively. The obtained cycle durations were close to the target cycle duration (i.e., 909 ms), suggesting that the subjects obeyed the metronome pacing.

FMRI Analysis

Analysis of the isolated performance conditions. The results of the group analysis for the contrasts WRIST – REST and FOOT – REST are presented in Table 1. Results of single subjects will not be discussed

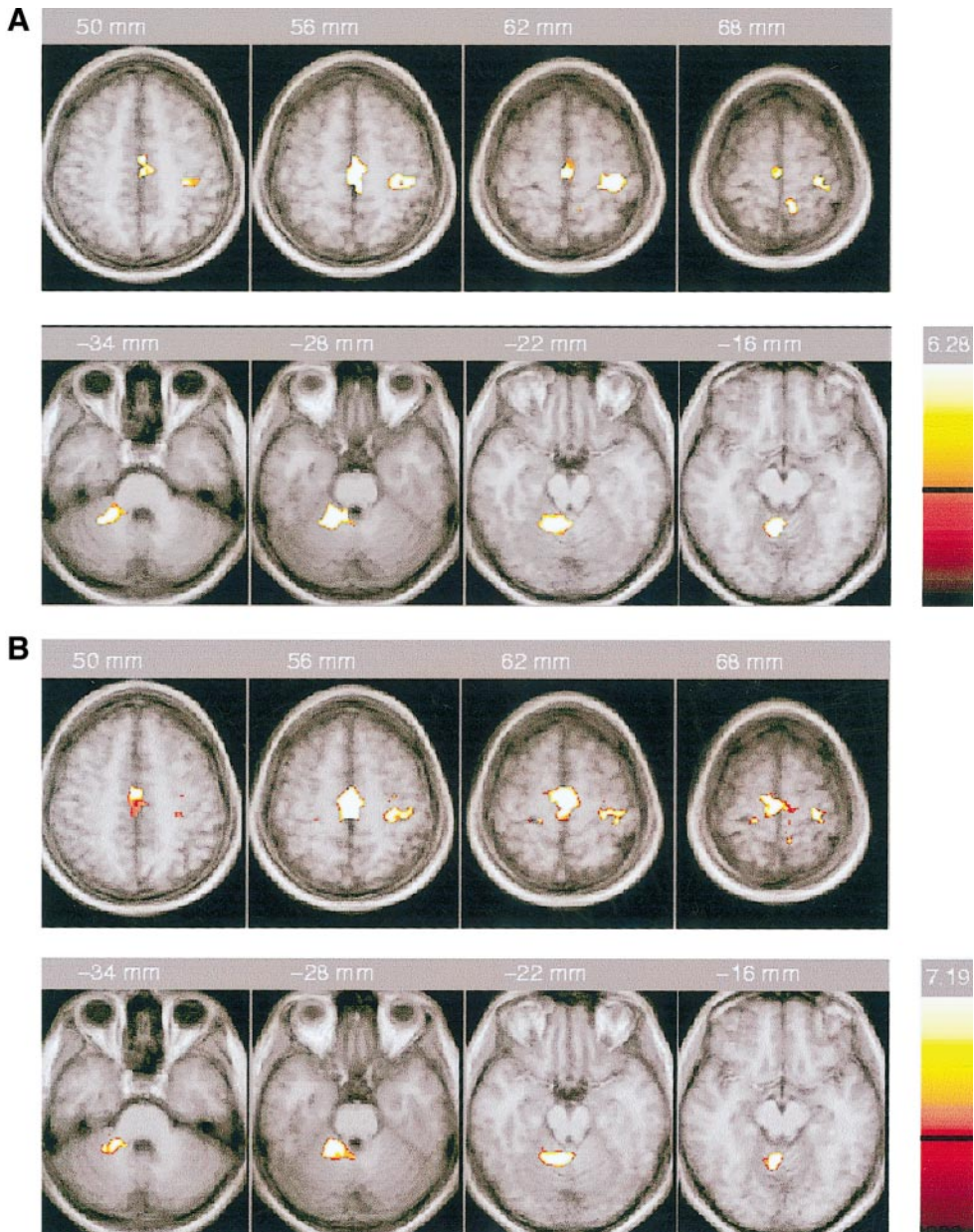


FIG. 2. Group SPMs for the contrasts (A) ISODIR – (WRIST + FOOT) and (B) NONISODIR – (WRIST + FOOT) overlaid on anatomical sections of the averaged brain images of the six subjects. The contrasts represent the supplementary activation associated with coordination as compared to the sum of activations from the isolated limb movements. The right side of the scans corresponds to the left side of the brain.

in detail because no additional information was gained from this analysis. Performance of cyclical wrist movement was associated with activation in the contralateral primary sensorymotor cortex located around the lateral side of the central sulcus. Activation was also present on the medial wall of the superior frontal gyrus, located posteriorly from the VCA-line. This corresponded to the supplementary motor area (SMA). Activation in the SMA was located mainly on the contralateral side of the moving limb. The activation on the medial wall also extended to the upper bank of the cingulate gyrus corresponding to Brodmann Area 24/

31. This activation in the cingulate motor area (CMA) was located mainly on the contralateral side. Activation was also present on the lateral convexity of the brain along the precentral sulcus (lateral Brodmann Area 6). This recorreponds to the premotor cortex (PMC). Finally, within the cerebellum the hemisphere and vermal portion of the anterior lobe was activated on the right side ipsilateral to the moving limb.

Apart from somatotopic differences, results were similar for the foot movements (contrast FOOT – REST; Table 1). The activation in the primary sensorymotor cortex for this contrast was located more me-

TABLE 1

Activated Brain Areas during Isolated Movements of the Limb Segments versus Rest Conditions

Area	Wrist – rest				Foot – rest			
	Z score	x	y	z	Z score	x	y	z
M1/S1 hand area	8.25	-42	-27	60				
foot area	8.02	-39	-21	69	8.11	-3	-42	69
PMC	8.77	-30	-15	72				
SMA proper (L)	7.05	-12	-18	72	8.31	-3	-24	72
(R)					7.25	3	-15	75
CMC BA24/31	7.22	-3	-18	51				
Cerebellum ant. lobe (R)	12.25	24	-45	-30	11.46	24	-36	-33
Cerebellar vermis	9.83	9	-54	-15	7.61	3	-45	-18
	8.04	3	-63	-24	6.71	3	-45	-9
Temp. Lobe BA22/38					5.94	-57	9	-3

Note. Z scores and localization of significant pixels in each area resulting from the group analysis ($n = 6$). Z scores correspond to voxels of peak activity in locations provided by stereotaxic coordinates (MNI template). Threshold: $Z = 4.75$ ($P < 0.05$ corrected). M1/S1, primary sensorimotor cortex; PMC, premotor cortex; SMA, supplementary motor area; CMC, cingulate motor cortex; BA, Brodmann area.

dio-posterior along the central sulcus compared to wrist movement. Activation of the supplementary motor area was more bilateral and extended to the border of the cingulate motor cortex, though no significant foci were found for this area during foot movements. No significant activation was observed in the premotor cortex. In accordance with WRIST – REST, activation in the cerebellum corresponded to the ipsilateral anterior lobe (vermis and hemisphere portion). Activation in the anterior lobe was located more anteriorly and slightly more medial compared to activation during hand movements, in accordance with the expected somatotopic representation (see also Nitschke *et al.*, 1996).

Analysis of the coordination patterns. The contrasts ISODIR – (WRIST + FOOT) and NON-

SODIR – (WRIST + FOOT) both revealed the extra brain activation associated with coordination of the limb segments as compared to movements of the isolated limbs, which was of particular interest (Z-scores are shown in Table 2, group SPMs in Fig. 2). Coordination of the limbs, either according to the isodirectional or nonisodirectional coordination mode, was associated with extra activation in the contralateral primary sensorimotor cortex as compared to individual limb movements. The activation was evident in both the hand and foot areas. Both contrasts revealed extra activation along the contralateral premotor cortex, with addition of ipsilateral activation for the nonisodirectional movements. Interlimb coordination was also associated with extra activation in the SMA: the effect was mainly ipsilateral during isodirectional co-

TABLE 2

Activations in Brain Regions Emerging from the Contrasts ISODIR – (WRIST + FOOT) and NON-ISODIR – (WRIST + FOOT)

Area	ISODIR – (WRIST + FOOT)				NON ISODIR – (WRIST + FOOT)			
	Z score	x	y	z	Z score	x	y	z
M1/S1 hand area	6.28	-30	27	60	6.01	-27	-24	69
foot area	4.8	-3	-42	69	5.12	-6	-37	75
PMC (L)	4.83	-21	-15	75	4.61	-15	-21	75
(R)					4.91	15	-15	75
SMA proper (L)					4.72	-3	-12	78
(R)	5.31	3	-18	75	7.19	6	-21	58
CMC BA24/31	5.81	3	-21	57	5.41	3	-9	51
Cerebellum ant. lobe (R)	6.06	21	-45	-27	5.78	18	-39	-30
Cerebellar vermis	5.74	6	-51	-15	5.28	6	-51	-18
	4.85	9	-42	-27				

Note. Z scores and localisation of significant pixels in each area resulting from the group analysis ($n = 6$). Z scores correspond to voxels of peak activity in locations provided by stereotaxic coordinates (MNI template). Threshold: $Z = 4.75$ ($P < 0.05$ corrected). M1/S1, primary sensorimotor cortex; PMC, premotor cortex; SMA, supplementary motor area; BA, Brodmann area.

ordination and more bilateral during nonisodirectional coordination (see Fig. 2). The additional activation in the SMA extended to the bilateral cingulate motor cortex (BA24/31) for both contrasts, with only the ipsilateral area surviving corrected threshold levels. The cerebellum also showed increased activation levels associated with coordination of the limbs: the right anterior lobe and vermis (ipsilateral to the moving limb) showed extra activation for both contrasts.

Isodirectional versus nonisodirectional coordination. The direct comparison of the nonisodirectional and isodirectional mode (contrast NONISODIR – ISODIR) showed a marginally significant activation focus in the right SMA (Z -score: 4.70, $P = 0.057$, $x = 9$, $y = -15$, $z = 63$), which was additionally activated during the nonisodirectional movements (see also Fig. 3).

The conjunction of the contrasts (NONISODIR – ISODIR) and (WRIST + FOOT)–REST was intended to reveal those regions commonly activated for both contrasts. More specifically, the conjunction shows those areas that are related to the increased difficulty level of the nonisodirectional mode and that are also involved in the execution of cyclical limb movements. Activation was found in the right SMA (ipsilateral to the moving limb) (Z -score: 6.66, $x = 6$, $y = -12$, $z = 63$) and the right cingulate motor cortex (Z -score: 5.05, $x = 9$, $y = -15$, $z = 54$) both part of the same activation cluster. Additional activation was also observed in the left superior temporal gyrus (Z -score: 5.59, $x = -57$, $y = 9$, $z = -3$), presumably related to metronome pacing. Furthermore, a region of interest analysis (ROI) focussed upon the anatomically defined SMA, confirmed higher activation levels of the right SMA during the nonisodirectional coordination mode as compared to the isodirectional coordination mode (Z -score = 4.46, $P < 0.05$ corrected for ROI of SMA, $x = 6$, $y = -14$, $z = 64$).

DISCUSSION

Kinematics of Limb Movements

Successful on-line kinematic recordings of the limb movements during the scanning sessions were achieved in this study. This allowed the post-hoc assessment of some primary movement parameters, involving movement amplitude, cycle duration and relative phase. Relative phase findings were in general agreement with previous studies, in which the isodirectional mode was found to be performed with a higher degree of accuracy/stability than the non-isodirectional mode (Baldissera *et al.*, 1982, 1991; Kelso and Jeka, 1992; Serrien and Swinnen, 1997; Swinnen *et al.*, 1995, 1997a). No differences in mean amplitude and cycle duration were observed across conditions. SD scores of amplitude and cycle duration, on the other hand, showed significant differences between the sin-

gle limbs and the nonisodirectional mode, and between the isodirectional and nonisodirectional mode. The outcome of this analysis allows us to conclude that any differences in brain activation across experimental conditions cannot be ascribed to mean amplitude and timing differences. This is not a trivial matter because specific movement parameters, such as movement rate, movement amplitude, etc., have been shown to affect the level and distribution of activation (Blinkenberg *et al.*, 1996; Rao *et al.*, 1996; Waldvogel *et al.*, 1999). However, differences in amplitude variability, cycle duration variability, and relative phase accuracy/stability between the isodirectional and nonisodirectional modes are inherent to the execution of both coordination patterns. This was then the primary focus of interest for establishing potential differences in brain activation.

Cyclical Movements of Individual Limb Segments

The present findings demonstrated that the cyclical flexion/extension of the separate limb segments required the activation of a distributed motor network, including the primary contralateral sensorimotor cortex, the supplementary motor area (SMA), the cingulate motor cortex (CMC), the premotor cortex (PMC), and the cerebellum. Aside from somatotopic specificity (Penfield and Boldrey, 1937), no major differences were observed between hand and foot movements, except for premotor activity, which was only present during wrist movements, and for the SMA, which displayed more bilateral activation during foot movements. The activation foci observed in the premotor cortex during hand movements were located within the precentral gyrus just behind the precentral sulcus, corresponding to lateral BA6. In general, PMC activity has been related to sensory triggered/guided movements (Wessel *et al.*, 1997). In primates, the PMC is composed of multiple areas, including the dorsal premotor area (PMd) and ventral premotor area (PMv) (Dum and Strick, 1991). The activation in our task was probably located within the PMv close to the M1 hand area but more ventrally. Stephan *et al.* (1995) found activation in the left PMv during imagined movements as well as during the actual execution of movements with the upper limbs.

The involvement of the SMA during performance of sequential movements has also been documented in a considerable number of other PET and fMRI studies (Colebatch *et al.*, 1991; Grafton *et al.*, 1992; Shibasaki *et al.*, 1993; Remy *et al.*, 1994; Deiber *et al.*, 1991, 1996; Wexler *et al.*, 1997; Van Oostende *et al.*, 1997; Sadato *et al.*, 1996; Catalan *et al.*, 1998). On the basis of cytoarchitectonical and functional differences, the SMA is divided into two distinct movement related areas, i.e., the pre-SMA and the SMA-proper. The SMA-proper is strongly connected to the precentral motor cortex and

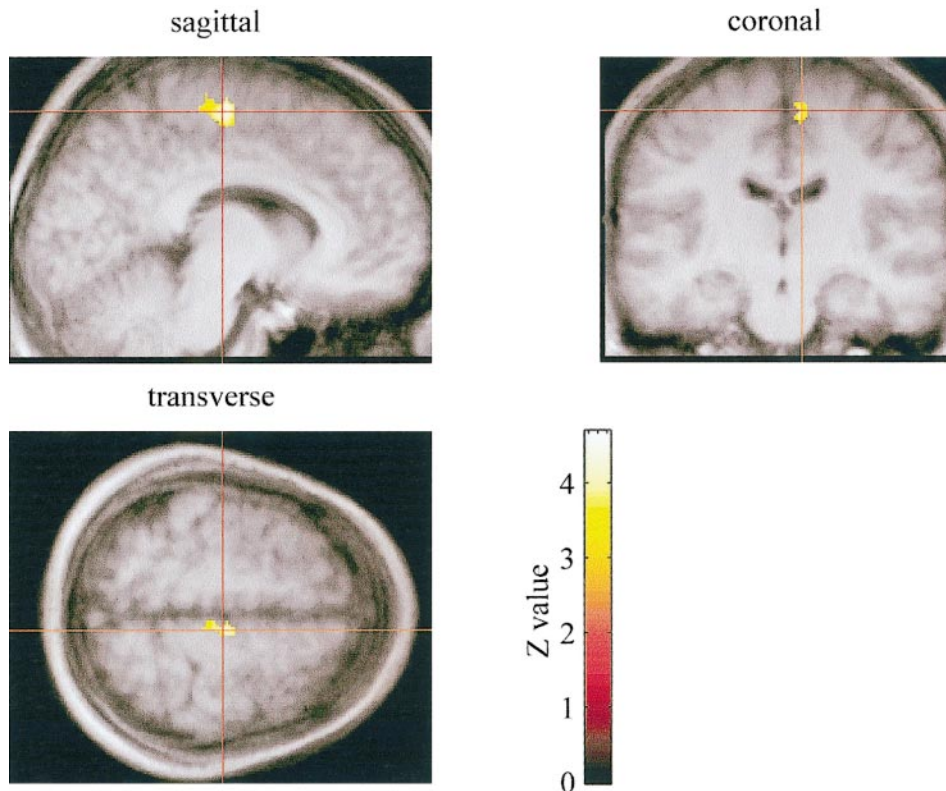


FIG. 3. Group SPM for the contrast NONISODIR – ISODIR overlaid on anatomical sections of the averaged brain images of the six subjects. The contrast shows increased activation for the right SMA (Z score: 4.70; $x = 9$, $y = -15$, $z = 63$) during nonisodirectional coordination versus isodirectional coordination. The right side of the scans corresponds to the right side of the brain.

has direct connections to the spinal cord whereas the pre-SMA is more strongly connected with the prefrontal lobe, the premotor cortex and anterior cingulate but not with the precentral motor cortex (Dum and Strick, 1991; Picard and Strick, 1996). The anterior SMA is more related to higher-order aspects of motor control such as preparation for movement (Deiber *et al.*, 1996) and selection of movements (Deiber *et al.*, 1991). Conversely, the activity of the SMA proper is associated with the execution of movements (Matelli *et al.*, 1993; Colebatch *et al.*, 1991). In the present study, the SMA activation foci were located within the SMA-proper behind the VCA-line, supporting the executive functions assigned to this area during the production of relatively simple tasks (Colebatch *et al.*, 1991; Matelli *et al.*, 1993; Tanji, 1994, 1996; Picard and Strick, 1996). Even though it has been proposed that the SMA is especially important for the production of 'internally' triggered movement (Rao *et al.*, 1993; Deiber *et al.*, 1991; Wessel *et al.*, 1997; Halsband *et al.*, 1993), we observed considerable SMA activity during metronome-paced movement conditions (see also Grafton *et al.*, 1992; Remy *et al.*, 1994).

Activation foci in the medial wall of the superior frontal gyrus also extended into the cingulate gyrus corresponding to Brodmann Area 24/31. The observed

combination of cingulate motor area and SMA-proper activation is not surprising as relatively strong connections have been identified between both areas (Tanji and Shima, 1994; Rizzolatti *et al.*, 1996). On the basis of PET findings, Picard and Strick (1996) proposed a division of the cingulate gyrus according to a simple/complex task dichotomy, i.e., a large rostral cingulate zone (RCZ) (further subdivided into two regions, each containing a body representation, i.e., RCZa and RCZp) activated in relation to complex tasks, and a caudal cingulate zone (CCZ) activated during more simple tasks. The rostral zone has been found to be significantly activated during selection (Deiber *et al.*, 1991) and imaging of movements (Stephan *et al.*, 1995), whereas the caudal zone has shown activation during a simple visual tracking task (Grafton *et al.*, 1993) and during execution of a joystick movement (Stephan *et al.*, 1995). The activation foci during the flexion-extension task of the hand in the present study were located in the caudal cingulate zone (BA24/31). This is in accordance with the relatively simple nature of the present task. The location of activation in the cingulate area was slightly more anterior than in the SMA-proper. During foot movement activation only reached the border of the cingulate cortex but did not further extend into this region.

In addition to the SMA and CMC, a rather robust activation was also observed in the cerebellum during isolated limb movements: Activation was found in the hemisphere and vermal portion of the anterior lobe ipsilaterally. The cerebellum has mainly been regarded as a motor organ (Brooks and Thach, 1981) involved in timing of movements (Ivry *et al.*, 1988), acquisition/discrimination of sensory information (Gao *et al.*, 1996; Jueptner *et al.*, 1996, 1997) and sensory information processing (Jueptner and Weiller, 1998). Recently, in accordance with our results, Shibasaki *et al.* (1993) reported PET activation in the anterior cerebellar hemisphere during sequential repetitive finger movements, whereas Grafton *et al.* (1992) concluded that the anterior cerebellar response is related to the execution of motor tasks, driven by external or internal cues. Furthermore, Sadato *et al.* (1996) observed that the activation in the right cerebellar anterior lobe did not increase as task complexity increased, underscoring its executive role in sequential finger movements. Our present findings are also in general agreement with early observations of Holmes (1939) who observed that patients with focal lesions of the cerebellum showed great difficulties in performing alternating movements such as pro-supination and flexion-extension. Accordingly, it can be concluded that the cerebellum is critically involved in the control of alternating sequential movements.

Coordination of Limb Segments

The critical comparisons for assessing the specific involvement of brain regions in the coordination of the limbs were ISODIR – (WRIST + FOOT) and NONISODIR – (WRIST + FOOT). As compared to the isolated movements of the limb segments, their coordination or synchronization was associated with an extra activation of the left primary sensorimotor cortex (contralateral foot and hand area), the right cerebellar anterior lobe and vermis, the premotor cortex, the right cingulate motor area and particularly the bilateral supplementary motor area. This clearly shows that coordination was not managed by a specific brain area but required a general increase in activation of a complete motor network that is distributed across cortical and subcortical regions.

The observed increased activation of the SMA during interlimb coordination is of particular interest because previous lesion and imaging studies in humans have associated this brain area with bimanual coordination, often in association with the cingulate motor area (Laplane *et al.*, 1977; Chan and Ross, 1988; Sadato *et al.*, 1997; Stephan *et al.*, 1999a, 1999b; Nirkko *et al.*, 1999; Jäncke *et al.*, 2000). Corresponding observations were made in non-human primates were long-lasting deficits in bimanual coordination were demonstrated after unilateral ablation of the SMA (Brinkman, 1981, 1984). The

present study showed that coordination of the ipsilateral wrist and foot was also associated with extra activation of the SMA and cingulate, in combination with other areas, as compared to the sum of activations observed during isolated limb movements. This suggests that the link that has traditionally been made between bimanual (homologous) coordination and the SMA should be abandoned and replaced by a more general role with respect to the coordination of various limb segments in which the SMA is involved as part of a larger network. These observations further strengthen recent concerns that have been raised with respect to the presumed (exclusive) role of the SMA in bimanual coordination (Donchin *et al.*, 1998; Kazennikov *et al.*, 1998, 1999; Kermadi *et al.*, 1998, 2000; Wiesendanger *et al.*, 1994).

Kermadi *et al.* (2000) suggested that at least five cortical areas may participate in the control of sequential bimanual movements, i.e., the premotor cortex, the cingulate motor cortex, the SMA, the posterior parietal cortex, and the primary motor cortex. This was confirmed by the current results showing increased levels of activation in these cortical areas, except for the posterior parietal cortex. In monkey, unique cells have been found in the primary motor cortex, for example, whose activity is specifically associated with bimanual movements (Donchin *et al.*, 1998). Furthermore, it has been also been observed that the primary motor cortex contains equal proportions of bimanually related neurons as the SMA (Donchin *et al.*, 1998; Kazennikov *et al.*, 1999; Kermadi *et al.*, 1998), suggesting a more direct role of the primary motor cortex in the process of interlimb coordination.

The present findings also underscore the long-standing role of the cerebellum in motor coordination (see news focus, Science, 1998, 281, 1588–1590). For example, Holmes already reported in 1939 that cerebellar lesioned patients encountered difficulties with reversing directions in two limbs at the same time. It appears that the cerebellum plays an important role in the execution of rapidly alternating, repetitive movements and in the execution of movements requiring the coordination of several extremities (Gilman, 1985), both being dominant features of the present ipsilateral coordination task. This activity may refer to both a motor and sensory role for the cerebellum. The observed extra activation of the cerebellum during coordination may also be related to its important role in movement timing (Ivry *et al.*, 1988) because coordination requires accurate timing and onset of muscle activity to produce synchronous movements of the limbs.

Finally, both coordination modes (isodirectional and nonisodirectional) were also compared to each other to identify differential activations. Behavioral studies have convincingly demonstrated that the nonisodirectional mode is generally produced with a lower degree of accuracy and consistency than the isodirectional mode (Baldissera *et al.*, 1982, 1991; Kelso and Jeka,

1992; Serrien and Swinnen, 1997; Swinnen *et al.*, 1995, 1997a), particularly in motor disordered patients (Swinnen *et al.*, 1997b; Baldissera, 1994). This was also confirmed by the spatiotemporal findings of the present study in which successful on-line kinematic recordings were made during fMRI scanning. The comparison of both modes revealed that the ipsilateral SMA (and cingulate motor cortex) showed an increased level of activation during the more difficult non-isodirectional mode as compared to the isodirectional coordination mode.

This suggests that the SMA and cingulate are becoming increasingly important when more difficult spatial relations between simultaneous limb movements have to be monitored, particularly when the coordination pattern is inherently unstable. Therefore, the role of the SMA may consist of a higher order on-line planning of the movement sequences as well as their synchronization. The observed differential activation levels are consistent with previous studies on bimanual coordination in which activation of the posterior SMA was found to be significantly larger during the less stable parallel than during mirror bimanual movements (Sadato *et al.*, 1997; Stephan *et al.*, 1999b). Accordingly, an interesting parallel appears to exist between bimanual and ipsilateral limb coordination.

In summary, the present study suggests that coordination of the ipsilateral limb segments (and possibly other forms of coordination) is not orchestrated by a specific command center or brain area but rather requires the increased involvement or collaboration among areas of a motor network, distributed across cortical as well as subcortical regions. Whereas it has become a textbook generalization to link the SMA with bimanual coordination, we conclude that the SMA is a primary motor cortical region that is substantially (but not exclusively) involved in the organisation and on-line control of coordination between the homologous as well as the nonhomologous limb segments.

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