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Simultaneous movements of upper and lower limbs are coordinated by motor representations that are shared by both limbs: a PET study

H. Henrik Ehrsson,[1,2] Eiichi Naito,[3] Stefan Geyer,[4] Katrin Amunts,[4] Karl Zilles,[4] Hans Forssberg[2] and Per E. Roland[1]
[1]Division of Human Brain Research and PET, Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden
[2]Motoriklab, Department of Woman and Child Health, Karolinska Institutet, Stockholm, Sweden
[3]Faculty of Human Studies, Kyoto University Sakyo-ku Kyoto 606-8501, Japan
[4]Department of Neuroanatomy and C. and O. Vogt Institute for Brain Research, University of Düsseldorf, Düsseldorf, Germany

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Abstract

The purpose of this study was to examine the cerebral control of simultaneous movements of the upper and lower limbs. We examined two hypotheses on how the brain coordinates movement: (i) by the involvement of motor representations shared by both limbs; or (ii) by the engagement of specific neural populations. We used positron emission tomography to measure the relative cerebral blood flow in healthy subjects performing isolated cyclic flexion–extension movements of the wrist and ankle (i.e. movements of wrist or ankle alone), and simultaneous movements of the wrist and ankle (a rest condition was also included). The simultaneous movements were performed in the same directions (iso-directional) and in opposite directions (antidirectional). There was no difference in the brain activity between these two patterns of coordination. In several motor-related areas (e.g. the contralateral ventral premotor area, the dorsal premotor area, the supplementary motor area, the parietal operculum and the posterior parietal cortex), the representation of the isolated wrist movement overlapped with the representation of the isolated ankle movement. Importantly, the simultaneous movements activated the same set of motor-related regions that were active during the isolated movements. In the contralateral ventral premotor cortex, dorsal premotor cortex and parietal operculum, there was less activity during the simultaneous movements than for the sum of the activity for the two isolated movements (interaction analysis). Indeed, in the ventral premotor cortex and parietal operculum, the activity was practically identical regardless whether only the wrist, only the ankle, or both the wrist and the ankle were moved. Taken together, these findings suggest that interlimb coordination is mediated by motor representations shared by both limbs, rather than being mediated by specific additional neural populations.

Introduction

Previous functional mapping studies investigating the motor system in humans have mainly focused on isolated movements of single limbs (Roland *et al*., 1980; Colebatch *et al*., 1991; Roland & Zilles, 1996; Fink *et al*., 1997). Yet, movements made in daily life usually involve several limbs or segments of the body. Some previous studies have investigated bimanual movements (Tanji *et al*., 1987; Sadato *et al*., 1997a; Donchin *et al*., 1998; Stephan *et al*., 1999), but there is no information available on how the brain controls simultaneous movements of the upper and lower limbs on the same side of the body.

Several authors have suggested that coordinated movements are controlled by specific structures of the brain, e.g. the cerebellum (Babinski, 1906; Nashner & Grimm, 1978; Dow, 1987; Thach *et al*., 1992), the lateral premotor cortex (Kleist, 1907; Luria, 1966; Freund, 1990) and the supplementary motor area (SMA, Brinkman, 1984). However, interlimb coordination could be mediated by mechanisms other than specific 'coordination centres'. Recent studies using functional magnetic resonance imaging (fMRI) have shown that isolated movements of the hand and isolated movement of the foot engage some common motor representations in the ventral premotor area (PMV), the parietal operculum (PO) and parts of the SMA (Ehrsson *et al*., 1999; Rijntjes *et al*., 1999). Possibly, such areas could coordinate movements of different limbs when the movements are performed simultaneously.

The purpose of the present study was to investigate some principal issues concerning the control of coordinated simultaneous movements of the upper and lower limbs. The first aim was to determine which areas of the brain control simultaneous movement. Secondly, we examined if the coordination of the simultaneous movements depends on specific neuronal populations in addition to those active during isolated movements. Thirdly, we investigated whether the control of the simultaneous movements engages motor representations that are shared by both limbs.

Behavioural studies have shown that when the wrist and ankle are moved simultaneously, they automatically couple either in the same direction (iso-directionally) or in opposite directions (antidirectionally, Kelso *et al*., 1979; Baldissera *et al*., 1982; Swinnen *et al*., 1997). There is evidence that initially the antidirectional movements are more difficult to perform (Baldissera *et al*., 1982; Swinnen *et al*., 1997). Another aim of the present study was therefore to explore the

Correspondence: H. Henrik Ehrsson, Division of Human Brain Research and PET, Department of Neuroscience, Karolinska Institutet, Berzeliusvägen 5, 171 77, Stockholm Sweden.
E-mail: henrike@mrc.ks.se

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possibility that the antidirectional and iso-directional simultaneous movements could be associated with different patterns of cortical activity.

We used positron emission tomography (PET) to measure the regional cerebral blood flow (rCBF) in healthy subjects making isolated movements of the wrist and ankle, or simultaneous movements of the limbs (iso-directional and antidirectional). First we detected those regions that, statistically, are active during each isolated movement, and which regions that were specific for movement of either limb or common to the two limbs. We then detected regions that were active when performing the simultaneous movements (both iso- and antidirectional). Finally, we tested for changes in activity specific to the control of the simultaneous movements by comparing the simultaneous movements with both of the isolated movements (interaction analysis), thereby eliminating the effects related to skeletomuscular activity.

Materials and methods

Subjects

Eight healthy male subjects with no history of neurological disease participated in the study. Their age ranged from 24 to 27 years. All subjects were strongly right-handed (Oldfield, 1971). The subjects had given their written consent and the study had been approved by the Ethical Committee and the Radiation Safety Committee of the Karolinska Hospital and was performed according to the guidelines of the Declaration of Helsinki 1975.

Tasks

The subjects performed five tasks while the relative rCBF was measured with PET. They rested comfortably in a supine position on the bed of the PET scanner. Each subject had his head fixed to the scanner with a stereotaxic helmet that restricted head movements (Bergström *et al.*, 1981). The right arm and leg were placed in comfortable positions, and we used appropriate supports to minimize the movement of proximal joints and other parts of the body. The extended right arm was supine and abducted 25° from the trunk. The right leg was flexed 30° in the hip joint and flexed 30° in the knee joint so that the lower leg was parallel to the scanner bed. The left arm and leg were extended in relaxed positions. The subjects were blindfolded and also instructed to keep their eyes closed. Metronome sounds were played at 1 Hz whilst the PET measurements were being conducted. The subjects were asked to relax completely, and to make no movement other than those they were instructed to make.

To perform the movement tasks, the subjects made cyclic flexion–extension movements of the right ankle and/or the right wrist. They were to perform a smooth continuous action through the whole range of the movement. The pace was set by the metronome and at each click sound the limbs were either maximally extended or completely flexed (i.e. each complete flexion–extension cycle took 2 s). Figure 1 shows the movements of the wrist and ankle for the different conditions together with the auditory cues. In the FOOT task, subjects made isolated movements of the right ankle. In the HAND task, subjects performed isolated movements of the right wrist. In the SIMULTANEOUS tasks, the subjects moved the right wrist and right ankle simultaneously. There were two such tasks: in the ISO-DIRECTIONAL task, the wrist and ankle were moved in the same directions in the sagittal plane (the wrist and the ankle flexed and extended together). In the ANTIDIRECTIONAL task, the joints were moved in opposite directions (when the wrist was flexed the ankle was extended and vice versa). Thus, SIMULTANEOUS task refers to all coordinated movements irrespectively of the movement direction. During the REST condition, the subjects heard the metronome, but made no movement.

Because the antiphase movements were initially somewhat difficult to perform, the subjects were trained prior to the PET scanning (the training lasted 30–45 min and was performed just before scanning). All tasks were practised. After the training all subjects could perform the requested antidirectional and iso-directional movements at 1.5 Hz or faster for 1 min. They could also make the iso-directional and antidirectional movements at 0.5 Hz while simultaneously performing a verb-generation task without any errors (no interference, Passingham, 1996). From this we concluded that all movement tasks were overlearned before the PET scanning started.

The movements were monitored with goniometers attached to the lateral aspect of the wrist and ankle. The goniometers were made of light plastic and did not restrict the movements. The recordings were stored digitally on a portable PC (DASport, PCI-20450P-14 using Visual Designer^{TM}) and subsequently analysed off-line (using ZOOM, Department of Physiology, Umeå University). We analysed the amplitude of the movement of the joints, the variability (SD) of the amplitudes, and the peak angular velocity of the movements. For the simultaneous movements we assessed the synchronization of the limbs with a correlation analysis of the wrist and ankle movements. We also assessed the synchronization of the limbs by measuring the time interval between the peaks in the maximal displacement of the wrist and ankle joints. A negative value indicated that the movement of the foot occurred earlier than the movement of the hand. We also monitored the performance with two video cameras to check for possible involuntary movements of other body parts; one was positioned to obtain the best view of the moving limbs on the right hand side and the other was positioned to give the best view of the left (non-moving) limbs. Surface electrodes were used to record electromyograms (EMGs) from the main flexor and extensor muscles of the wrist (M. flexor carpi radialis and M. extensor carpi radialis) and ankle (M. tibialis anterior and M. gastrocnemius, Myo115-electrodes, Liberty Technology, Hopkinton, MA, USA). EMGs were also recorded from the flexor muscles of the left wrist and ankle to check for muscle activity in the non-moving limbs. The EMG signals were recorded, stored and displayed on-line (DASport, PCI-20450P-14 and Visual Designer^{TM}).

Brain scanning

Each subject, equipped with a stereotaxic helmet (Bergström *et al.*, 1981), underwent magnetic resonance imaging (MRI) and PET. An anatomical high-resolution T1-weighted MRI scan was collected on a 1.5 T GE scanner (Signa Horizon Echospeed, General Electric Medical Systems, Milwaukee, Winsconsin) equipped with a head-coil (3D-SPGR; TE = 5 ms; TR = 21 ms; flip angle = 50°; FOV = 256 mm; matrix, 256 × 256; 124 slices).

The relative rCBF was measured with an ECAT EXACT HR PET camera operating in three-dimensional mode (for technical description see Weinhard *et al.*, 1994). The subjects had a catheter placed into the right brachial vein for tracer administration. Each participant underwent 15 PET scans. Each experimental condition was repeated three times and the order of the conditions followed a pseudo-randomized schedule to balance out possible time effects. For each scan, ~13 mCi of ^{15}O-butanol was injected intravenously as a bolus. The radiotracer was synthesized according to the method of Berridge *et al.* (1991). Images of the relative rCBF were generated by summing the activity during

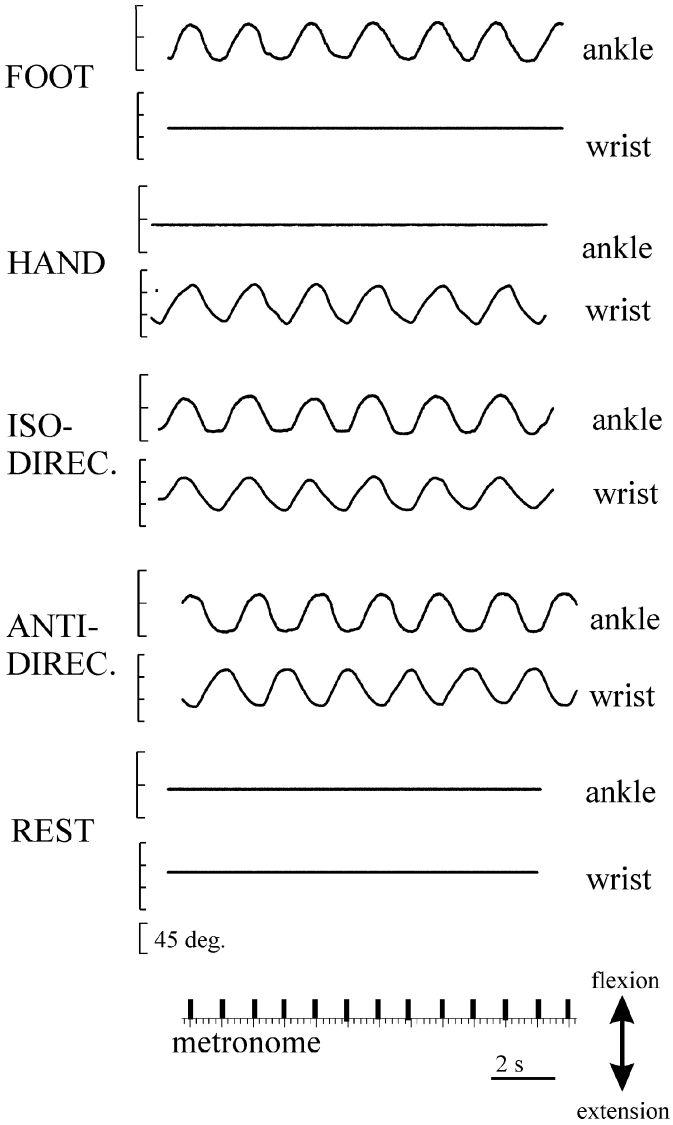

FIG. 1. The displacement of the right wrist and right ankle in the five conditions. The subjects made cyclic flexion–extension movements. Representative goniometer recordings are shown from one subject. A metronome (at 1 Hz) paced the movements; the auditory cues are indicated.

the 50 s immediately following the first increase in cerebral activity after the intravenous injection. The PET scans were reconstructed with a 4-mm Hanning filter.

Image processing and statistical analysis

Each subject's PET scans were spatially aligned to the first scan (Friston *et al*., 1995a). Then each individual's anatomical MRI was spatially transformed to the standard anatomical format in the Human Brain Atlas (HBA 1999 standard brain, Roland *et al*., 1994). The PET images were then transformed to the HBA format using the same transformations. Linear and non-linear transformations were used, and special care was taken to optimize the fit of the central sulcus. In the standard format the coordinates refer to the stereotactic coordinate system of Talaraich & Tournoux (1988). The PET scans were reformatted to a voxel size of $2 \times 2 \times 2$ mm and voxels outside the brain were excluded from the analysis. The PET scans were spatially smoothed with a 10-mm (FWHM) Gaussian filter to increase the signal to noise ratio. Global changes in the activity were removed by applying linear scaling. The mean rCBF value was then arbitrarily set to 50 mL/100 g/min. The PET images of the eight subjects were analysed as a group.

The statistical analysis was performed with the general linear model (GLM, Friston *et al*., 1995b; Ledberg *et al*., 1998). For every voxel the activity was modelled as a linear sum of factors in a design matrix. The design matrix had tasks, repetitions and subjects as factors. By estimating the task-specific effects using linear contrasts in the GLM, we created statistical images with a *Z*-distribution. These statistical images were subsequently arbitrarily thresholded at $Z > 3.09$ at each voxel. The thresholded *Z*-images have many clustered voxels (clusters) with high *Z*-values in those regions for which there is a large difference in the activity level for the contrasted tasks. The activations were then characterized in terms of peak height and spatial extent. We only report those activations with an extent corresponding to a value of $P < 0.05$ or better after correction for the number of multiple comparisons within the whole brain space (omnibus $P < 0.05$). The critical size of the activated clusters corresponding to this level of significance was estimated using the method developed by Ledberg (2000). This method uses Monte Carlo simulations ($n = 5000$) on synthetic noise images, taking into account the physiological auto-correlation, to derive the probability that a given cluster size would occur by chance. From this we determined the threshold to be 1440 mm^3 for the critical size for significant clusters and we adopted this as our significance criterion. All reported clusters were also found to correspond to a corrected $P < 0.05$ when we used SPM-96 (Friston *et al*., 1994; http//:HTTP://www.fil.ion.ucl.ac.uk/spm). Because the activated areas were so extensive when the movement tasks were contrasted with the rest condition, we also report activations on the basis of peak height ($P < 0.05$) after a correction for multiple comparisons in the whole brain space (Friston *et al*., 1995b, as implemented in SPM-96).

We compared the different conditions by defining contrasts in the GLM. We employed pair-wise comparisons, a conjunction analysis and an interaction analysis (see below).

Firstly, we contrasted each movement task (HAND, FOOT, SIMULTANEOUS, ISO-DIRECTIONAL and ANTIDIRECTIONAL) versus the rest condition (REST). The activation maps showed the regions that were active when performing each task. Secondly, we determined which motor regions were specific (somatotopic) to either limb when the contrasts (HAND versus FOOT) and (FOOT versus HAND) were analysed. Then thirdly, we characterized the areas common to the movement of either limb with a conjunction analysis (Price *et al*., 1997). The conjunction analysis identified those regions that are significantly ($P < 0.05$ corrected for multiple comparisons) commonly active for both movement of the wrist versus rest, and movement of ankle versus rest, and that do not show a significant interaction between these conditions ($Z < 3.09$ for each voxel). This analysis was limited to those voxels that were found to be active for both (HAND versus REST) and (FOOT versus REST) (by a masking procedure, $Z > 3.09$). Fourthly, we compared the coordinated movements performed in different directions, i.e. (ISO-DIRECTIONAL versus ANTIDIRECTIONAL) movements and (ANTIDIRECTIONAL versus ISO-DIRECTIONAL) movements. It can be noted here that both of these simultaneous movements activated identical brain regions (for details, see Results). Fifthly, we used an interaction analysis (factorial design) in which pairs of conditions were contrasted (for discussion on interaction analyses and recent applications see Price *et al*., 1997; Rees *et al*., 1997; Blakemore *et al*., 1998; Fink *et al*., 1999). The interaction analysis tests whether the activity when performing movements simulta-

neously is different from the sum of the activities of the two isolated movements. We defined the contrast (SIMULTANEOUS – REST) – {(HAND – REST) + (FOOT – REST)} to test for increases in activity, and the contrast {(HAND – REST) + (FOOT – REST)} – (SIMULTANEOUS – REST) to test for attenuated responses specifically related to the simultaneous movements. Importantly, in these comparisons, the number of movements of each limb is matched to eliminate (or 'factor out') the effects related to muscular activity. Hence, this analysis detects effects specifically related to the context of the movements, i.e. it identifies activity specific to how the actions were performed: simultaneously or in isolation. Finally, we analysed the contrasts (SIMULTANEOUS versus HAND) and (SIMULTANEOUS versus FOOT). These tests show areas with stronger activity when two limbs were moved compared to when one limb only was moved. Note, however, that these comparisons are not matched for the motor output and therefore do not reveal changes in activity specific to coordination.

Defining the functional and anatomical regions

Changes in rCBF from the PET experiment were compared with the location of the statistically defined cytoarchitectonic areas 4a, 4p, 3a, 3b, 1 and 44 (Geyer *et al*., 1996, 1999; Amunts *et al*., 1999). The cytoarchitectonic regions were delineated with observer-independent techniques in a population of nine post mortem brains, and were subsequently transformed into the same standard anatomical format (HBA) as the functional images had been using the same type of linear and non-linear transformations (Roland *et al*., 1994; for details about the anatomical delineation see Amunts *et al*., 1999; Geyer *et al*., 1999; Schleicher *et al*., 1999). Corresponding areas from different brains were superimposed in standard three-dimensional space and spatially filtered with a 5-mm (FWHM) Gaussian filter. Overlay maps were calculated for each area (Roland & Zilles, 1998). These overlay maps are referred to as population maps describing, for each voxel in standard anatomical space, how many brains that have one particular cytoarchitectural area located at that voxel. We use these population maps to estimate the likelihood that a particular location (voxel) in standard anatomical space corresponds to a certain area. In this study we define each cytoarchitectural area in standard space as the 50% population map of that area, i.e. the volume in which the voxels correspond to that area in $\geqslant 50\%$ of the post mortem brains (Roland & Zilles, 1998, for applications of this method and further documentation see Naito *et al*., 1999; Larsson *et al*., 1999; Bodegård *et al*., 2000). Because there is little correspondence between gross morphology and the locations of cytoarchitectural areas, these 50% population maps are currently the only way to describe the location and extent of these areas in a valid way (Roland *et al*., 1997; Roland & Zilles, 1998). Finally, the rCBF changes were compared with the location of the cytoarchitectural areas. For peaks of activity located outside, but close to, a 50% population map of a cytoarchitectural area, we report the number of post mortem brains that had a representation of that area at that location.

The premotor cortex and the SMA were defined arbitrarily. By the SMA, we mean the cortex rostral to area 4a on the medial side of the hemisphere, above the cingulate sulcus. The rostral border of the SMA was defined as the vertical plane at $y = 16$ (Buser & Bancaud, 1967). In the present study all the activations were located in the SMA posterior to $y = 0$, which probably corresponds to the classical SMA (or SMA-proper) (Picard & Strick, 1996; Roland & Zilles, 1996). The lateral premotor cortex, divided into a dorsal (PMD) and ventral (PMV) portion, is located rostral to lateral area 4a (Geyer *et al*., 1996; Roland & Zilles, 1996). The rostral border of the PMD is not known. The PMV was defined as the cortex posterior to area 44 and anterior to area 4a. The border between the PMD and the PMV was defined as a horizontal plane at $z = 45$ in this population of subjects. The cingulate motor areas (CMAs) and their preliminary parcellation into a rostral part (CMAr) and a caudal part (CMAc) were described in Roland & Zilles (1996).

The anatomical localizations of the activations in other parts of the brain were related to the major sulci and gyri distinguishable on a mean MRI generated from the standardized anatomical MRIs from the eight subjects (Ono *et al*., 1990).

Results

Behaviour

During PET scanning, all subjects performed the requested movements at the pace of the metronome (0.5 Hz) without any errors. The mean amplitude of the wrist movements was 90.7 ° (13.2) (mean of means ± SD of means for all subjects) across all tasks, and of the ankle movements 44.3 ° (16.0) across all tasks. The mean amplitude of the wrist movements was 91.0 ° (7.5) (mean of means ± SD of means) in the HAND task, 87.5 ° (10.5) in the ISO-DIRECTIONAL task, and 93.7 ° (19.5) in the ANTIDIRECTIONAL task. The mean amplitude for movements of the ankle was 44.2 ° (15.4) in the FOOT task, 44.8 ° (14.7) in the ISO-DIRECTIONAL task, and 43.8 ° (14.7) in the ANTIDIRECTIONAL task. There were no significant differences in the amplitude of the movement for the different tasks ($P > 0.05$ paired *t*-tests).

The average peak angular velocity was 101.8 °/s (26.1) (mean of means ± SD of mean, for all subjects) for the ankle movements across all tasks, and 237.3 °/s (71.7) for the wrist movements across all tasks. There were no significant differences in the movement velocity between the different tasks.

The variability of the amplitude (mean SD) of the ankle movements was significantly larger in the ANTIDIRECTIONAL task [4.29 ° (1.51); mean SD ± SD of mean SD] than in the ISO-DIRECTIONAL task [2.43 ° (0.82)] or in the FOOT task [2.32 ° (0.70)] ($P < 0.05$ paired *t*-tests). There were no significant differences in the variability of the wrist movements for any of the tasks ($P > 0.05$ paired *t*-test).

Correlation analysis showed a high degree of synchronization for the simultaneous movements (mean of absolute values 0.889 ± 0.109). There was a higher degree of synchronization during the ISO-DIRECTIONAL task (mean 0.973 ± 0.016) than during the ANTIDIRECTIONAL task (mean –0.789 ± 0.074) ($P > 0.05$, paired *t*-test using absolute values). The mean intervals between the peak amplitudes of the wrist and ankle movements were –64 ms (33) (mean of means ± SD of means) in the ISO-DIRECTIONAL task and –73 ms (47) in the ANTIDIRECTIONAL task, i.e. the maximum displacement of the ankle occurred slightly earlier than the maximum displacement of the wrist. These differences between the coordination tasks were not significant ($P > 0.05$ paired *t*-tests).

The EMGs of the main flexor and extensor muscles showed similar levels of muscle activity for the different tasks. There was no muscle activity and the video recordings revealed no movements in the left (non-moving) limbs. During the rest condition we did not observe or record any movements or muscle activity in any limbs.

Isolated movements of the limbs

Active regions specific to the movement of either limb

Table 1 and Fig. 2 show the brain regions that displayed a significant increase in the relative rCBF when we contrasted isolated movement of either limb with the rest condition [(HAND versus REST) and

TABLE 1. Isolated and simultaneous movements versus rest

Functional region (cytoarchitectural area, anatomical region)	Talaraich coordinates (HBA)			Peak Z-score	Volume (cm^3)
	x	*y*	*z*		
FOOT versus REST					
Left SMA/M1[a], posterior part of superior frontal gyrus	6	–23	68	8.79	57.5
Right paracentral lobule	–10	–45	68	6.29	
SMA, right superior frontal gyrus	–6	–5	48	8.18	
Right anterior cerebellum	–12	–37	–16	7.22	12.2
Left parietal operculum	42	–29	24	6.82	
Left putamen	32	–11	12	5.27	
Left PMV, precentral sulcus[b]	54	5	22	4.97	
Left thalamus	12	–17	8	5.00	
Right parietal operculum	–44	–23	24	4.92	1.62
HAND versus REST					
Left M1, area 4a	32	–29	54	8.64	72.1
Left PMD/M1, precentral gyrus[c]	32	–29	64	8.57	
SMA, left superior frontal gyrus	6	–9	51	7.83	
Left parietal operculum	42	–25	24	7.02	
Left thalamus	12	–17	6	5.99	
Left superior parietal gyrus	18	–57	64	5.91	
Right PMD, anterior precentral gyrus	–26	–13	68	5.66	
Right PMD, precentral sulcus	–36	–9	58	5.46	
SMA, right superior frontal gyrus	–12	–13	56	4.66	
Left PMV, precentral sulcus[d]	56	5	26	4.55	1.16
Right parietal operculum	–46	–21	22	5.55	2.13
Right insula	–36	–9	14	4.62	
Right anterior cerebellum	–16	–45	–16	7.80	15.6
Left anterior cerebellum	22	–53	–20	4.72	1.84
SIMULTANEOUS versus REST					
Left SMA/M1[e]	8	–23	70	9.04	240
Left M1, area 4a	32	–29	56	8.70	
Left PMD, precentral gyrus	26	–21	68	8.52	
SMA, superior frontal gyrus	6	–9	50	8.51	
Right anterior cerebellum	–16	–43	–16	8.36	
Left parietal operculum	40	–27	24	7.30	
Right paracentral lobule	–8	–47	66	7.10	
Left thalamus	12	–19	8	7.06	
Left putamen	26	–5	8	6.97	
Cerebellum, vermis	–2	–57	–28	6.67	
Right PMD, superior precentral sulcus	–24	–15	70	6.07	
Right parietal operculum	–42	–25	26	5.86	
Right postcentral sulcus	–28	–35	46	5.15	
Right parietal superior gyrus	–32	–43	62	4.92	
Left anterior cerebellum	20	–43	–20	4.86	
Right PMD, precentral sulcus	–34	–7	56	4.65	
Left insula	38	–3	16	4.59	

Significant increases in relative rCBF ($P < 0.05$ corrected for multiple comparisons). Anatomical locations refers to the mean standardized anatomical MRI. Cytoarchitectural areas were defined in nine standardized post mortem brain (see Materials and methods). Note that positive *x*-coordinates indicate the left hemisphere. [a]Located just anterior to area 4a. Area 4a in 3/9 post mortem brains. [b]Located posterior to area 44. Area 44 in 3/9 post mortem brains. [c]Located just anterior to the anterior and lateral borders of area 4a. Area 4a in 4/9 post mortem brains. [d]Peak corresponds to a corrected $P = 0.056$. We report this peak descriptively. Located posterior to area 44. Area 44 in 2/9 post mortem brains. [e]Located anterior to area 4a. Area 4a in 1/9 post mortem brains.

(FOOT versus REST)] ($P < 0.05$ corrected for multiple comparisons). Isolated movements of the hand and isolated movements of the foot engaged different sections of the contralateral primary motor cortex (M1) (4a, 4p), primary sensory cortex (S1) (1, 3b) and the ipsilateral anterior cerebellum. Figure 3 and Table 2 show the regions that were specific (somatotopic) for either limb when we contrasted isolated movement of the wrist versus isolated movements of the ankle, and vice versa. The activated cluster in the M1 region specific to the wrist extended from $y = -55$ in the superior parietal lobule to $y = -3$ in the precentral sulcus (PMD). The activated cluster specific to the ankle extended from $y = -44$ in the paracentral lobule to $y = -1$ in the SMA.

Active regions common to the movement of either limb

Both isolated movement of the wrist and isolated movement of the ankle activated the contralateral thalamus, the putamen, and, bilaterally, the SMA and the lateral PO when compared with the rest condition (Fig. 2 and Table 1). Isolated movement of the ankle activated the contralateral PMV ($P < 0.05$ after correction for multiple comparisons), while the contralateral PMV activation during isolated wrist movements did not reach the significance criterion ($Z = 4.55$, $P = 0.055$, after a correction for multiple comparisons using a test for peak-height, Friston *et al*., 1995b). Yet, we still choose to report this foci descriptively to show the similarities with the foot activation. The local maxima of the PMV activation were located just posterior to the 50% population map defining area 44. The activated cluster extended both anteriorly and posteriorly, into area 44 and into the precentral gyrus, respectively. Hand movements also activated the PMD bilaterally. When subjects moved the right foot, activity extended into the PMD from the medial wall activation (see Fig. 2, top row).

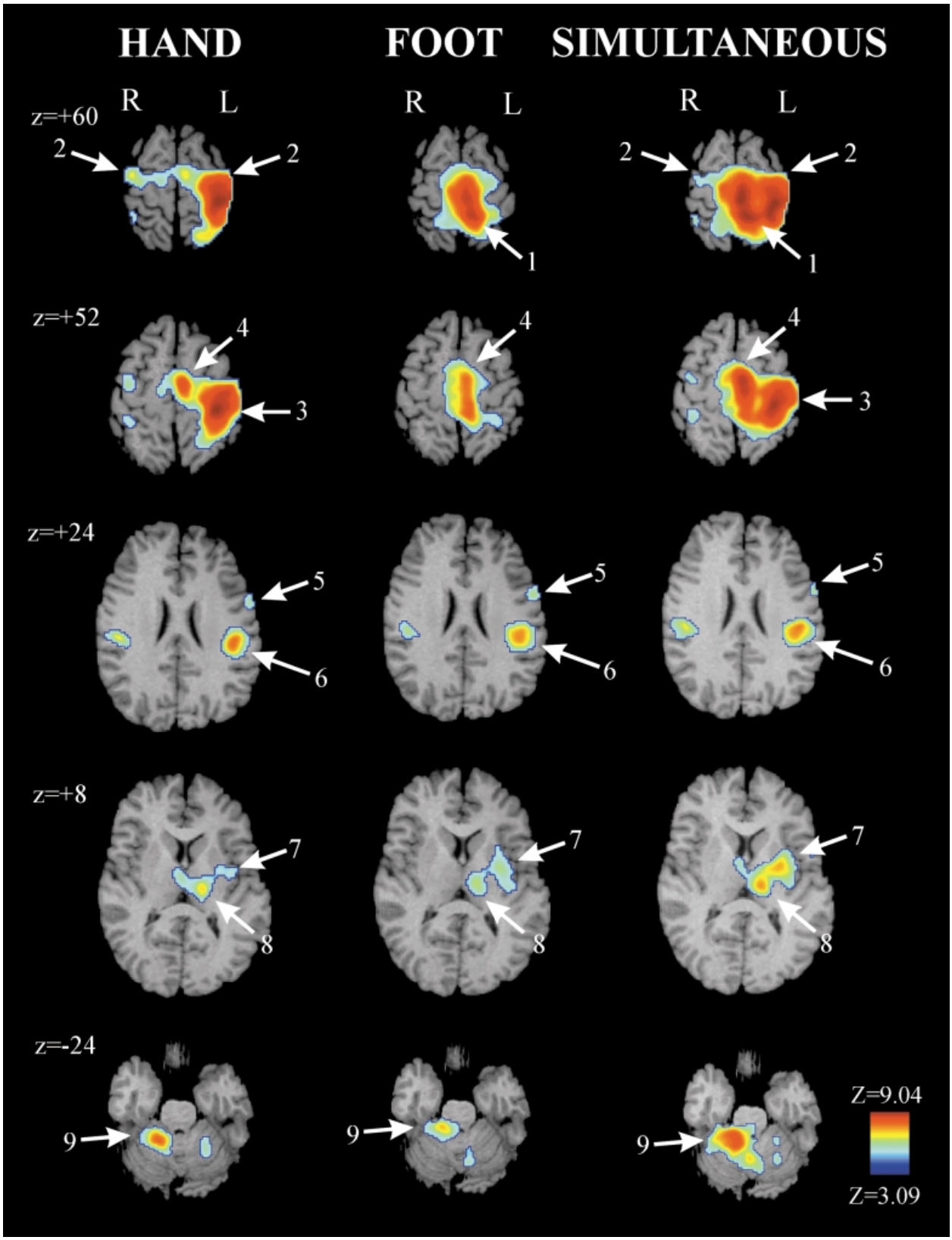

FIG. 2. From left to right, the columns represent the brain activity detected when making isolated movements of the right wrist (HAND versus REST), the right ankle (FOOT versus REST) and simultaneous movements of the two limbs (SIMULTANEOUS versus REST). Significant increases in the relative rCBF ($P < 0.05$ corrected for multiple comparisons) are superimposed on the standard brain (HBA). Each row displays an axial slice and the Talaraich coordinates are indicated. Some relevant functional regions are identified by numbers: 1, primary motor cortex (foot section); 2, dorsal premotor cortex; 3, primary motor cortex (hand section); 4, supplementary motor area; 5, ventral premotor cortex; 6, parietal operculum; 7, putamen; 8, thalamus; 9, anterior cerebellar hemisphere.

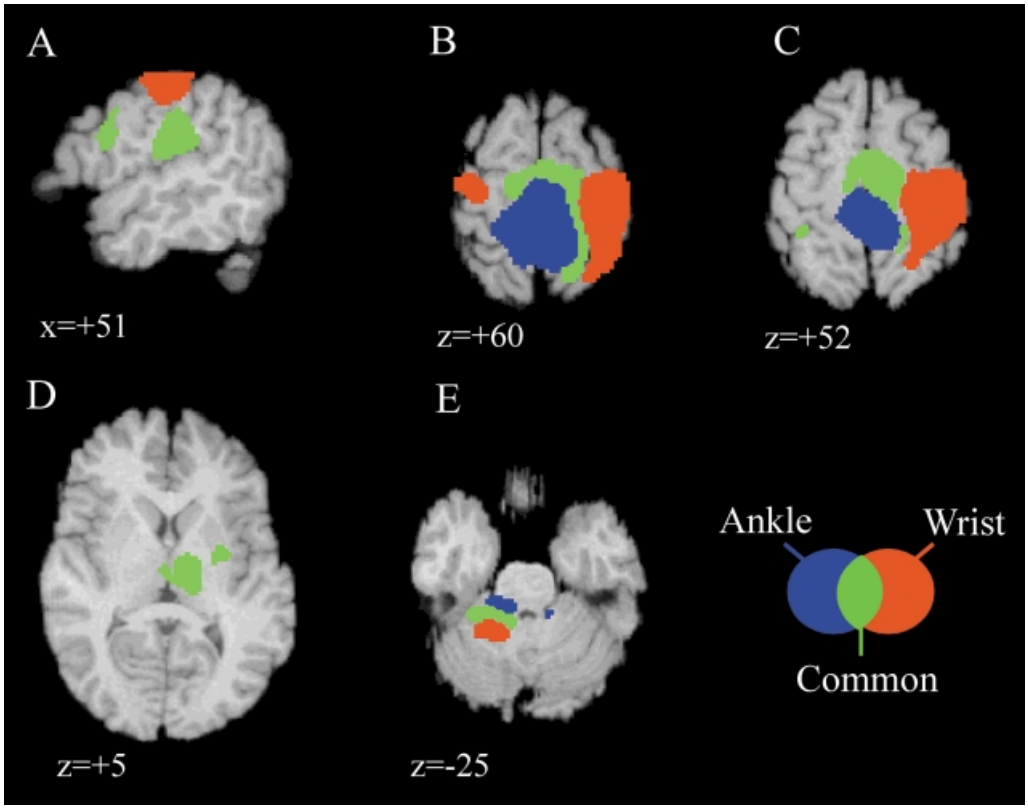

FIG. 3. Regions that were common or specific (i.e. somatotopic) for isolated movement of the right wrist and isolated movement of the right ankle (A–E). Significant activations for HAND versus FOOT are shown in red, FOOT versus HAND in blue, and common areas in green (conjunction analysis). The results are superimposed on the HBA standard brain ($P < 0.05$ corrected for multiple comparisons). The Talaraich coordinates are indicated for each slice. See also Table 2

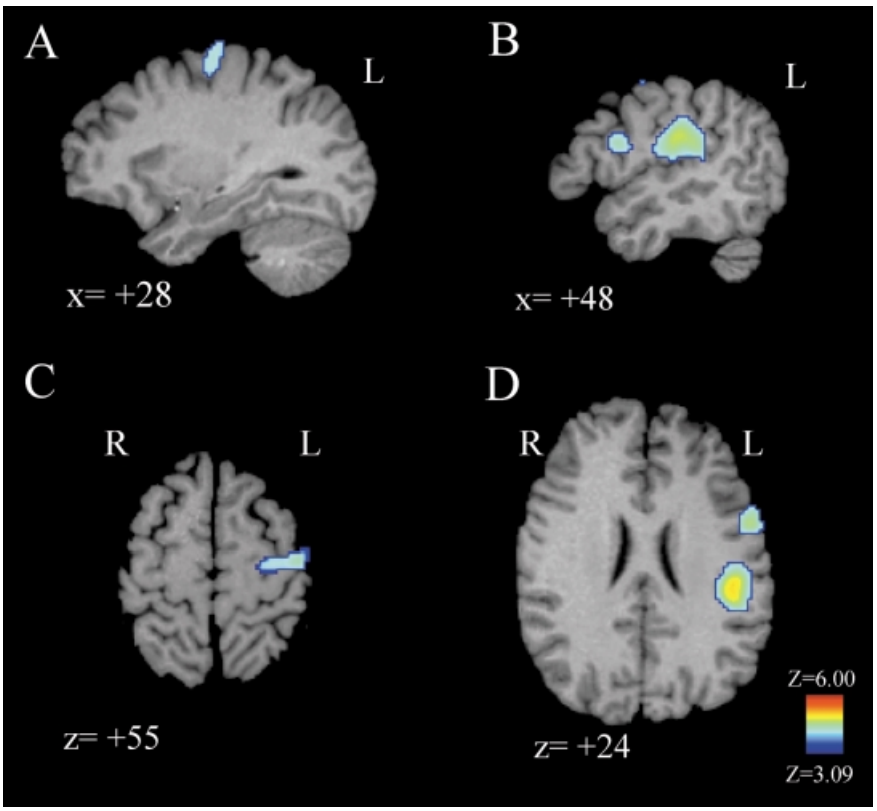

FIG. 4. Regions that showed less activity for simultaneous movements compared with the sum of the activities for both isolated movements {$P < 0.05$ corrected for multiple comparisons: [(HAND – REST) + (FOOT – REST)] – (SIMULTANEOUS – REST)}. In the contralateral PMV (B and D) and PO (B and D) this meant that the activity was almost identical regardless of whether only the wrist, only the ankle or both limbs were moved. In the PMD (A and C), the activity evoked by isolated wrist movement was somewhat larger than when the wrist was moved in combination with the foot. See also Fig. 5.

TABLE 2. Specific and common regions for wrist and ankle

Functional region (cytoarchitectural area, anatomical region)	Talaraich coordinates (HBA)			Peak *Z*-score	Volume (cm^3)
	x	*y*	*z*		
HAND versus FOOT					
Left M1, area 4a	32	–27	54	8.64	25.3
Left PMD/M1, left precentral gyrus[a]	34	–29	64	8.62	
Right anterior cerebellum	–22	–45	–20	6.02	4.85
Left anterior cerebellum	14	–50	–18	5.83	
Right PMD, right precentral sulcus	–30	–15	62	4.94	1.78
FOOT versus HAND					
Left SMA/M1, left precentral gyrus[b]	4	–23	68	8.64	32.2
Left M1, area 4a	10	–35	68	8.46	
Right M1, area 4a	–12	–35	68	7.13	
Right anterior cerebellum	–12	–33	–18	5.93	3.31
Common regions (conjuction analysis)[c]					
Left SMA	6	–9	52	8.68	14.4
Left SMA	14	–19	72	8.32	
Left postcentral sulcus	26	–39	64	7.72	
Left precuneus	14	–55	64	6.05	
Right SMA	–10	–15	58	5.77	
Right PMD, superior precentral sulcus	–20	–13	68	4.90	
Left parietal operculum	42	–14	12	7.97	7.96
Left insula	34	–11	14	5.25	
Left putamen	28	–5	8	4.81	
Left PMV, precentral sulcus	54	5	24	5.21	0.86
Left thalamus	12	–17	8	6.23	3.24
Right anterior cerebellar hemisphere	–14	–41	–16	8.00	3.60
Right parietal operculum	–46	–23	22	5.96	1.12

Significant increases in relative rCBF ($P < 0.05$ corrected for multiple comparisons). Anatomical locations refers to the mean standardized anatomical MRI. Cytoarchitectural areas were defined in nine standardized post mortem brains (see Materials and methods). Note that positive *x*-coordinates indicate the left hemisphere. [a]Located just anterior to area 4a. Area 4a in 3/9 post mortem brains. [b]Located just anterior to area 4a. Area 4a in 3/9 post mortem brains. [c]Regions commonly active for both isolated wrist movement versus rest and isolated ankle movement versus rest (see Materials and methods).

In Fig. 3 and Table 2 we show the results from the conjunction analysis testing for regions in common to isolated movement of the wrist and isolated movement of the ankle. The activations included the contralateral PMV, PMD, superior parietal cortex (postcentral sulcus and precuneus), thalamus and putamen, and part of the right anterior cerebellar hemisphere (a region between the somatotopic fields). In addition, the bilateral SMA and lateral PO were commonly engaged when moving either limb.

Simultaneous movements of the limbs

Simultaneous movements versus rest

Figure 2 and Table 1 show that simultaneous movements activated the same set of regions that was active during the isolated movements [(SIMULTANEOUS versus REST), $P < 0.05$ corrected for multiple comparisons]. This included activity in the contralateral M1, S1 (hand and foot sections), SMA, putamen and thalamus, PMD, bilateral PO and the ipsilateral anterior cerebellar hemisphere. The activation extended into the contralateral PMV (with a local maxima at $x = 54$, $y = 5$, $z = 22$, $Z = 3.84$, $P > 0.05$ after correction for multiple comparisons). As presented in detail below, the iso-directional and antidirectional movements activated identical brain regions.

Changes in activity specific for simultaneous movements (interaction analysis)

We compared the simultaneous movements with both isolated movements in the interaction analysis. There was no increase in activity specifically related to the coordination of the simultaneous movements, i.e. none was identified with the contrast (SIMULTANEOUS – REST) – {(HAND – REST) + (FOOT – REST)}. This was confirmed by using a descriptive very liberal statistical threshold ($Z < 2.58$, no clusters were found of extent $> 200\,mm^3$). On the contrary, we found lower activity levels during the simultaneous movements than expected in several sensory and motor regions. Table 3 and Fig. 4 show a significant interaction effect when we compared both isolated movements with the simultaneous movements using the contrast {(HAND – REST) + (FOOT – REST)} – (SIMULTANEOUS – REST) ($P < 0.05$ corrected for multiple comparisons). These effects were located in the contralateral PMD, PMV and PO. Figure 5 shows the plotted normalized relative rCBF for these areas for the different tasks. In the PMV and PO, the activity was practically identical regardless of whether only the wrist, only the ankle, or both the wrist and ankle were moved. In the PMD, the activity evoked by isolated wrist movement was somewhat higher than when the wrist was moved in combination with the foot. Hence, the interaction analysis has shown that, for these three areas, the sum of the activities for both of the isolated movements was stronger than the activity measured during the simultaneous movements.

It can be noted that we obtained equivalent results from the interaction analysis when we used the ISO-DIRECTIONAL task or the ANTIDIRECTIONAL task instead of the SIMULTANEOUS tasks (not shown).

Simultaneous movement versus isolated movement of one limb only

In Table 4 we list the results from the comparison of simultaneous movement versus isolated movement of the hand, or isolated movement of the foot, respectively [(SIMULTANEOUS versus HAND) and (SIMULTANEOUS versus FOOT)]. We detected stronger activity for SIMULTANEOUS versus HAND in contralateral M1 and SI (foot section), the right anterior cerebellar hemisphere (foot section) and the SMA. SIMULTANEOUS versus FOOT gave increases in rCBF in contralateral M1 and S1 (hand

TABLE 3. Interaction analysis

Functional region (cytoarchitectural area, anatomical region)	Talaraich coordinates (HBA)			Peak Z-score	Volume (cm^3)
	x	*y*	*z*		
{(HAND – REST) + (FOOT – REST)} – (SIMULTANEOUS – REST)					
Left parietal operculum	44	–25	24	4.72	7.81
Left PMV, precentral sulcus[a]	52	5	24	4.77	1.81
Left PMD, precentral sulcus	42	–11	54	4.29	2.21

The sum of the activities for both isolated movements was significantly stronger than the activity measured whilst performing simultaneous movements (interaction effect, $P < 0.05$ corrected for multiple comparisons). Anatomical locations refers to the mean standardized anatomical MRI. Cytoarchitectural areas were defined in nine standardized post mortem brains (see Materials and methods). Note that positive *x*-coordinates indicate the left hemisphere. [a]Located posterior to area 44. Area 44 in 2/9 post mortem brains.

section), the right anterior cerebellum (hand section) and the SMA. Because these comparisons are not matched in terms of the skeletomotor output, they do not reveal increases in activity specific to the coordination of the limbs. For the SMA this was demonstrated by the fact that there was a statistical trend for less activity during SIMULTANEOUS then for the sum of the activities for HAND and FOOT (interaction analysis, $Z = 4.16$, $P < 0.25$ after a correction for multiple comparison at $x = 6$, $y = -10$, $z = 50$), which rules out the possibility that the activity in SMA specifically reflected interlimb coordination.

Antidirectional and iso-directional movements

Table 5 lists the regions that were significantly activated when we contrasted ISO-DIRECTIONAL versus REST, and ANTI-DIRECTIONAL versus REST ($P < 0.05$ corrected for multiple comparisons). The iso-directional and antidirectional movements engaged the same set of sensorimotor regions with only small differences in the locations and occurrences of the local maxima of activity that could be detected. Importantly, when we contrasted the two tasks directly, we found no significant differences in activity anywhere in the brain [(ANTIDIRECTIONAL versus ISO-DIRECTIONAL), or (ISO-DIRECTIONAL versus ANTIDIRECTIONAL)]. To exclude the possibility that this lack of difference merely reflected the conservative statistical threshold used, we also examined the activity of known motor sections of the brain (M1, PM, SMA, anterior and posterior parietal cortex, striatum and cerebellum) using a more liberal statistical criterion. In a purely descriptive approach, we used the threshold of $Z > 2.58$ for the *Z*-images, but still no trends for increases in activity were found (i.e. no clusters larger than 200 mm^3 were found). From this we conclude that there were no relevant differences in the level of rCBF between the two coordination patterns.

Principal component analysis

To further confirm that the activity patterns during the iso-directional and antidirectional coordinated movements were the same, we applied a singular value decomposition (principal component or eigenimage analysis) to the adjusted rCBF data (Friston *et al.*, 1993). This descriptive method characterizes the changes in the variance–covariances introduced by the experimental design and can give further information about changes in activity in both the spatial and temporal domains. For each subject we used three average scans generated from the ISO-DIRECTIONAL, ANTIDIRECTIONAL and REST conditions, respectively. The result of this analysis is principal components that can be described in a spatial domain (eigenimage) and a profile over the conditions (condition loading). The first principal component (i.e. the eigenimage) could explain 96.9% of the total variance–covariance structure. The conditional loadings for the first principal component showed that it represented the differences between both the simultaneous movements and the rest condition. The positive component of this first principal component represented a functional network of well-known motor-related areas, including the primary sensori-motor region (hand and foot sections), PMD, PMV, SMA, PO, superior parietal cortex, putamen, thalamus and cerebellum (not shown). This set of regions corresponded to all the areas that we found to be active in the statistical analysis when we contrasted the simultaneous movements with the rest condition. The second principal component was very small (3.1% of the total variance–covariance structure) and the conditional loadings showed that this was related to differences between the iso-directional and antidirectional movements. These changes were small and spatially widely distributed and were not localized to any relevant sensorimotor-related brain regions. From these results and those of the statistical analysis, we conclude that the iso-directional and antidirectional movements were associated with practically identical activation maps.

Discussion

This is the first functional mapping study that has investigated the cerebral control of simultaneous movements of the upper and lower limbs. One of the principle findings is that simultaneous movements of limbs are coordinated by the same regions that control each of the limbs when moved separately. Thus, the coordination of the limbs is not dependent on any additional specific brain structure. On the contrary, in contralateral PMV, PMD and PO, the activity measured while the simultaneous movement was being performed was less than the sum of the activity for the isolated movements (interaction effect, $P < 0.05$ after correction for multiple comparisons). Importantly, several of the motor representations controlling simultaneous movements (e.g. the contralateral PMV, the anterior part of the PMD, the SMA, the PO and the posterior parietal cortex) were active for isolated movement of the wrist and ankle. In conclusion, these findings indicate that coordination of the wrist and ankle is mediated by cortical areas shared by both limbs, rather than being controlled by specific additional neural populations.

In all tasks the subjects executed smooth continuous cyclic flexion–extension movements of the right wrist and ankle. To perform the simultaneous movements it was required that the speed and position of the wrist and ankle were synchronized so that a constant phase relationship was maintained throughout each cycle. This synchronization of the limbs was not required when making the individual movements of wrist or ankle. Thus, during the simultaneous movements the subjects had to coordinate the movements in addition to generating the individual movements. Before the brain scanning started, the subjects were trained in performing the tasks until they could make the requested movements in a relaxed manner.

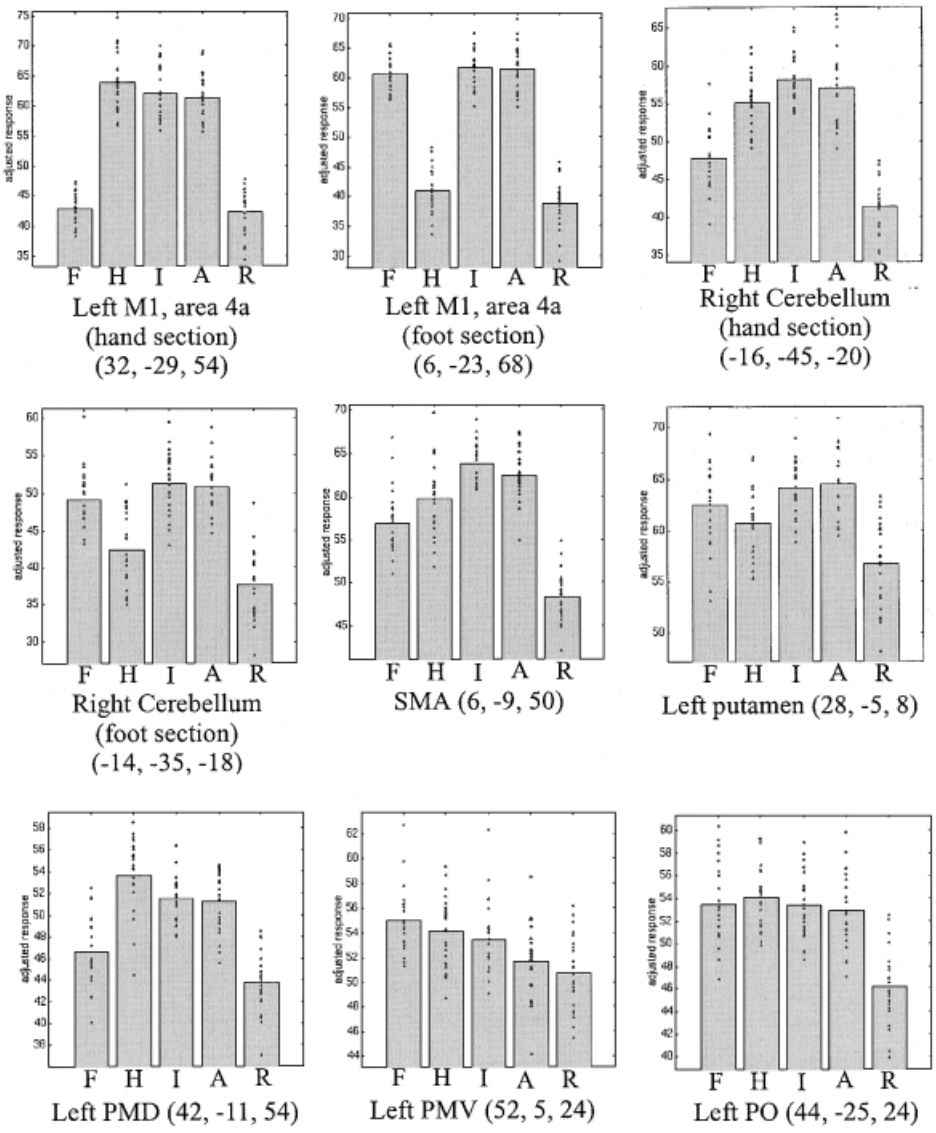

FIG. 5. Adjusted relative rCBF values (adjusted responses) in some relevant motor regions. Note the similar responses in the PMD, PMV and PO in the bottom row evoked by movements of the wrist only, the ankle only, and wrist and ankle simultaneously. The *Z*-value and Talaraich coordinates for each peak of activity are indicated. The experimental conditions are indicated by letters: F, FOOT; H, HAND; I, ISO-DIRECTIONAL; A, ANTIDIRECTIONAL; R, REST.

This ensured that the tasks were well matched in terms of general difficulty and that no motor learning occurred during the scanning. We monitored the performance during the scanning and found no significant differences in the amplitude or the velocity of the movements between the tasks. A metronome paced the movements and metronome-clicks were also present for the rest condition. Thereby, the effects of the auditory stimuli were matched.

The present study was not designed to investigate somatotopy. Previous PET and fMRI studies have suggested that it is preferential to do this by examining the activation patterns of single subjects (Grafton *et al*., 1993; Nitschke *et al*., 1996; Fink *et al*., 1997; Kleinschmidt *et al*., 1997; Ehrsson *et al*., 1999). Activation maps derived from a population of subjects might obscure subtle changes in the location of some activations because of the averaging of the functional anatomy across subjects, spatial filtering applied to the images, and image standardization procedures.

One of the topics of particular interest in this study was to examine changes in activity specifically related to the control of simultaneous movements. To investigate this we applied an interaction analysis which localizes non-additive (i.e. non-linear) effects when comparing the activity during two simultaneously performed movements with the sum of the activities for the isolated movements. Neuronal populations encoding movement of particular segments of the body are found not only in the M1, but also in a number of premotor and parietal areas, as well as in subcortical structures (Penfield & Boldrey, 1937; Thach *et al*., 1992; He *et al*., 1993, 1995; Rizzolatti *et al*., 1998). Thus, if each limb was controlled independently by somatotopic neuronal populations, then simultaneous movements would engage the neuronal populations of both limbs. One would then anticipate that the sum of the activations for the two isolated movements would correspond to the activation during the simultaneous movements. Areas exhibiting a pattern of activity that does not correspond with this expectation (the null hypothesis) can then be identified statistically in the interaction analysis. The principal finding in the present study was that in several sensorimotor-related areas (contralateral PMV, PMD and PO) the activity levels during the simultaneous movements were less than expected, i.e. less than the sum of the activity measured during isolated movements of the wrist and ankle. This suggests that combined movements of two body parts on the same side of the body are efficiently controlled by the supraspinal centres with relatively little demand for additional cortical processing (see below).

A related methodological concern is whether we can exclude the possibility that the relative rCBF becomes 'saturated' (i.e. reaches a 'ceiling') during the isolated movements and therefore does not show

TABLE 4. Simultaneous movements versus movement of one limb alone[c]

Functional region (cytoarchitectural area, anatomical region)	Talaraich coordinates (HBA)			Peak Z-score	Volume (cm^3)
	x	*y*	*z*		
SIMULTANEOUS versus HAND					
Left SMA/M1, posterior part of superior frontal gyrus[a]	4	–23	68	8.90	49.3
Left M1, area 4a	12	–42	66	8.63	
Left CMA, cingulate sulcus	8	–3	44	5.59	
Right cerebellar hemisphere	–12	–35	–18	7.02	16.8
Right putamen	26	–5	12	4.22	2.24
SIMULTANEOUS versus FOOT					
Left PMD/M1, precentral gyrus[b]	32	–27	64	8.69	35.0
SMA, left superior frontal gyrus	6	–9	50	6.38	
Right anterior cerebellar hemisphere	–16	45	–16	7.35	16.5

Significant increases in relative rCBF ($P < 0.05$ corrected for multiple comparisons). Anatomical locations refers to the mean standardized anatomical MRI. Cytoarchitectural areas were defined in nine standardized post mortem brain (see Materials and methods). Note that positive *x*-coordinates indicate the left hemisphere. [a]Located just anterior to area 4a. Area 4a in 3/9 post mortem brains. [b]Located just anterior to area 4a. Area 4a in 2/9 post mortem brains. [c]Comparisons are not matched for the skeleto-muscular output and thus, do not detect activity-specific for coordination *per see* (see Materials and methods).

any additional increases during the coordinated movements. Given the fact that the frequency of the movements in the present tasks was slow (0.5 Hz), and that previous studies have shown almost linear increases in the relative rCBF in motor areas (M1 and SMA) for frequencies of up to 2 Hz (Sadato *et al*., 1997b), it should be possible to discount this concern.

The functional representation of simultaneous movements of the upper and lower limbs

When the subjects performed isolated movements of either limb we found activity in a multitude of well-known sensorimotor regions, in agreement with previous functional mapping studies (Roland *et al*., 1980; Colebatch *et al*., 1991; Grafton *et al*., 1991; Nitschke *et al*., 1996; Roland & Zilles, 1996; Fink *et al*., 1997; Kleinschmidt *et al*., 1997). Also in agreement with earlier work, we detected somatotopic activity in the contralateral primary sensorimotor cortex and the ipsilateral anterior cerebellar hemisphere (Grafton *et al*., 1991; Nitschke *et al*., 1996; Fink *et al*., 1997; Kleinschmidt *et al*., 1997). An interesting result was that isolated movements of each limb activated common cortical representations in contralateral PMV, the SMA, the PMD, the PO, and the anterior and posterior parietal cortex. This finding supports the observations of Rijntjes *et al*. (1999), who found that in the PMV, PO and part of the SMA, the representations of simple isolated finger movements (zigzag movements) overlapped with the representations of simple isolated foot movements. In addition we also found that the representations of the two limbs overlapped in the thalamus, putamen and part of the right cerebellar hemisphere. However, for these small subcortical regions we can not exclude the possibility that the overlap is caused by the limited anatomical resolution of the PET images.

An important and novel finding of the present study was that the simultaneous movements of the upper and lower limbs engaged the same regions of the brain as were active when making isolated movements of the same limbs. This included the motor representations in the lateral premotor cortex (left PMV, and a rostral section of PMD) and SMA, as well as activity in the parietal lobe (left PO, postcentral sulcus and precuneus) that were common for the wrist and ankle. Electrophysiological and anatomical studies in non-human primates suggest that the SMA, PMD and perhaps the PMV include representations of both the upper and lower limbs (Mitz & Wise, 1987; Barbas & Pandya, 1987; Gentilucci *et al*., 1988; Kurata, 1989; He *et al*., 1993; Dum & Strick, 1996). The existence of projections to the lumbar and cervical enlargements (He *et al*., 1993; Galea & Darian-Smith, 1994; Dum & Strick, 1996) and to M1 (Muakkassa & Strick, 1979; Stepniewska *et al*., 1993; Tokuno & Tanji, 1993) suggests that these regions are involved in the control of movements made by the hand and foot. Because our PET data showed that there was no specific region dedicated to the control coordinated movements, and because there are practically no direct anatomical connections between the sections of M1 controlling hand and foot movements (see, e.g. Ghosh *et al*., 1987), the common representations in these non-primary motor areas could play an important role for mediating interlimb coordination.

We did not detect any increases in the relative rCBF specifically related to coordination anywhere in the brain when the simultaneous movements were compared with the two isolated movements (there were not even any weak statistical trends, for details see Results). This contrasts with the commonly held conception that combined movements would require specific 'coordination centres' for their execution. It should be noted, however, that the spatial resolution of imaging techniques, e.g. PET does not allow us to examine the possibility that small subpopulations of neurons encode coordination-specific parameters within those regions we found active. However, our data strongly suggest that simultaneous movements of upper and lower limbs are coordinated by the macro-anatomical regions of the brain that control isolated movements.

Control of simultaneous versus isolated movements

In contralateral PMV, PMD and PO, the activity during the simultaneous movements of the limbs was less than the sum of the activities of both of the isolated movements [i.e. {(HAND – REST) + (FOOT – REST)} – (SIMULTANEOUS – REST), $P < 0.05$ corrected for multiple comparisons]. In the PMV and PO, this interaction meant that the activity was almost identical regardless of whether only the wrist, only the ankle, or both limbs were being moved. In the PMD, the activity evoked by moving the upper limb was attenuated when simultaneously moving the ankle. The pattern of responses in PMV and PO and the fact that these regions were commonly active for isolated movement of either limb, indicate that these areas are shared by the two limbs whilst performing simultaneous movements. This is because, if each limb was being controlled by separate neuronal populations within these areas (but perhaps not anatomically separable in our PET images), the level of activity would have increased. The task of the subjects in the present study was to perform rather similar flexion–extension movements with the right wrist and ankle. Thus, a motor program for these movements

TABLE 5. Iso-directional and antidirectional movements versus rest

Functional region (cytoarchitectural area, anatomical region)	Talaraich coordinates (HBA)			Peak *Z*-score (cm^3)	Volume
	x	*y*	*z*		
ISO-DIRECTIONAL versus REST					
Left SMA/M1[a]	6	–23	68	8.85	159
Left M1, area 4a	30	–29	56	8.54	
Left PMD, precentral gyrus[b]	32	–27	66	8.53	
SMA, left superior frontal gyrus	6	–9	50	8.35	
Right anterior cerebellum	–16	–45	–15	8.17	
Left parietal operculum	44	–23	24	6.70	
Left thalamus	12	–19	8	6.47	
Cerebellum, vermis	0	–59	–14	6.35	
Left putamen	26	–5	8	6.23	
Left postcentral sulcus	–14	–41	66	6.13	
Cerebellum, vermis	–2	–57	–28	6.07	
Left anterior cerebellum	20	–41	–20	4.95	
Right PMD, superior precentral sulcus	–24	–13	70	4.99	
Right parietal operculum	–44	–23	24	5.16	3.55
ANTIDIRECTIONAL versus REST					
Left SMA/M1[c]	8	–23	68	8.86	123
Left M1, area 4a	32	–29	62	8.45	
SMA, left superior frontal gyrus	6	–9	48	8.20	
Left parietal operculum	38	–27	22	7.16	
Right paracentral lobule	–8	–47	64	6.89	
Left thalamus	14	–17	8	6.70	
Left putamen	26	–3	8	6.58	
Right PMD, precentral gyrus	–26	–15	66	5.91	
Right parietal operculum	–42	–25	24	5.49	
Right superior parietal gyrus	–30	–45	60	4.87	
Right PMD, precentral sulcus	–34	–5	54	4.64	
Right anterior cerebellum	–16	–43	–18	8.09	38.5
Cerebellum, vermis	–2	–57	–28	5.83	

Significant increases in relative rCBF ($P < 0.05$, corrected for multiple comparisons). Anatomical locations refers to the mean standardized anatomical MRI. Cytoarchitectural areas were defined in nine standardized post mortem brain (see Materials and methods). Note that positive *x*-coordinates indicate the left hemisphere. [a]Located anterior to area 4a. Area 4a in 3/9 post mortem brains. [b]Located anterior to area 4a. Area 4a in 1/9 post mortem brains. [c]Located anterior to area 4a. Area 4a in 3/9 post mortem brains.

could be shared by the two limbs, and the specification of which muscles should be used could take place 'downstream' in the motor system (Lashley, 1930; Luria, 1966). Hence, the PMV activation in the present study displays the characteristics that would be expected of a region involved in generalized motor control (Lashley, 1930; Luria, 1966), i.e. the encoding of movement irrespective of the skeletomuscular elements involved. The PMV activation was located just posterior to the population map of cytoarchitectural area 44, which is the tentative location of area 6. In the monkey brain this region is highly interconnected (Preuss & Goldman-Rakic, 1989) with the somatosensory and motor representations in the PO (Robinson & Burton, 1980a,b; Ledberg *et al.*, 1995; Ehrsson *et al.*, 2000; Disbrow *et al.*, 2000). Thus, the similar patterns of activity detected in PMV and PO are in accordance with the anatomical connectivity between these areas described in the monkey.

There is a possibility that the lack of further increase in activity during the simultaneous movements could reflect additional demands for motor control during isolated movements. The vast majority of the movements we perform in daily life are executed as components of compound movements involving different segments of the body. Hence, the 'default' for the cerebral motor system could be to control combined movements. Behavioural studies of patients with brain lesions have shown that involuntary synergistic movements of non-moving limbs are more often seen in patients with cortical lesions, suggesting that the ability to perform purely isolated movements is associated with a high demand on cortical control (Cambier & Dehen, 1977; Woods & Teuber, 1978; Chiang & Lu, 1990). It is therefore tempting to speculate that some of the cortical activity associated with isolated movements reflects additional processing needed for this type of movement.

Although the movements in the present study involved fractionated movements of muscles on the distal part of the limbs, which is thought to be highly dependent on cortical control (Passingham, 1993), some aspects of the coordination of the limbs might be mediated at the spinal level via the propriospinal system or via the branching of supraspinal fibres to different segments of the spinal cord (Miller *et al.*, 1973, 1975; Abzug *et al.*, 1974; Armand & Aurenty, 1977; Shinoda *et al.*, 1979).

Antidirectional versus iso-directional coordinated movements

There was no difference in the pattern of cortical activity when the simultaneous movements were performed in the same (iso-directional) or opposite directions (antidirectional). Thus, the direction of the movements seems to be of little importance in terms of increases in rCBF. This was also confirmed by descriptively examining the data using liberal statistical thresholds and by a principal component analysis. In this experiment the coordinated movement tasks were well learned before the brain scanning so the performance, kinematics and overall difficulty of the tasks were well matched. Although the behavioural studies of Baldissera (Baldissera *et al.*, 1982) and Swinnen (Swinnen *et al.*, 1997) suggest that the anti- and iso-directional movements are controlled differently by the central nervous system (CNS), and we recorded larger variability of the movement amplitudes ($P < 0.05$ for ankle movements) and less synchronization of the limbs (correlation analysis, $P < 0.05$) for the antidirectional

movements, our PET data show that anti- and iso-directional movements depend on the same regions of the brain.

It needs to be pointed out that these findings do not exclude the possibility that antidirectional movements performed under more demanding conditions could be associated with additional increases in brain activity, e.g. when performed at very high frequencies. Behavioural studies have shown that antidirectional movements performed at high frequencies show non-stable performance and occasional transitions into the iso-directional pattern (Baldissera *et al*., 1982, 1991).

The result of the present study supposedly contrasts with the results from two recent functional mapping studies comparing mirror-like (in-phase) and parallel (antiphase) bimanual movements (Sadato *et al*., 1997a; Stephan *et al*., 1999). In these reports, stronger responses were recorded from the medial wall areas (including the SMA) during the antiphase movements. One important difference between the present study and the previous investigations is that bimanual coordination involves interhemispheric coupling, which is known to be mediated by the SMA (Rouiller *et al*., 1994), whereas this mechanism is unlikely to play a role for movements of the ipsilateral wrist and ankle.

Acknowledgements

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Abbreviations

CMAs, cingulate motor areas; CNS, central nervous system; EMGs, electromyograms; fMRI, functional magnetic resonance imaging; GLM, general linear model; MRI, magnetic resonance imaging; PET, positron emission tomography; PMD, dorsal premotor area; PMV, ventral premotor area; PO, parietal operculum; rCBF, regional cerebral blood flow; SMA, supplementary motor area.

References

Abzug, C., Maeda, M., Peterson, B.W. & Wilson, V.J. (1974) Cervical branching of lumbar vestibulospinal axons. *J. Physiol. (Lond.)* , **243**, 499–522.

Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H.B.M. & Zilles, K. (1999) Broca's region revisited: cytoarchitecture and intersubject variability. *J. Comp. Neurol.*, **412**, 319–341.

Armand, J. & Aurenty, R. (1977) Dual organization of motor corticospinal tract in the cat. *Neuroscience Lett.*, **6**, 1–7.

Babinski, J. (1906) Asynergie et inertie cerebelleuses. *Revue Neurologique*, **14**, 685–686.

Baldissera, F., Cavallari, P. & Civaschi, P. (1982) Preferential coupling between voluntary movements of ipsilateral limbs. *Neuroscience Lett.*, **34**, 95–100.

Baldissera, F., Cavallari, P., Marini, G. & Tassone, G. (1991) Differential control of in-phase and anti-phase coupling of rhythmic movements of ipsilateral hand and foot. *Exp. Brain Res.*, **83**, 375–380.

Barbas, H. & Pandya, D.N. (1987) Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. *J. Comp. Neurol.*, **256**, 211–228.

Bergström, M., Boethius, J., Eriksson, L., Greitz, T., Ribbe, T. & Widen, L. (1981) Head fixation device for reproducible position alignment in transmission CT and positron emission tomography. *J. Computer Assisted Tomogr.*, **5**, 136–141.

Berridge, M.S., Adler, L.P., Nelson, A.D., Cassidy, E.H., Muzic, R.F., Bednarczyk, E.M. & Miraldi, F. (1991) Measurement of human cerebral blood flow with [^{15}O]butanol and positron emission tomography. *J. Cereb. Blood Flow Metab.*, **11**, 707–715.

Blakemore, S.J., Wolpert, D.M. & Frith, C.D. (1998) Central cancellation of self-produced tickle sensation. *Nature Neuroscience*, **1**, 635–640.

Bodegård, A., Ledberg, A., Geyer, S., Naito, E., Zilles, K. & Roland, P.E. (2000) Object shape differences reflected by somatosensory cortical activation. *J. Neurosci.*, **20** (RC51), 1–5.

Brinkman, C. (1984) Supplementary motor area of the monkey's cerebral cortex: short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. *J. Neurosci.*, **4**, 918–929.

Buser, P. & Bancaud, J. (1967) Bases techniques et methodoliques de exploration fonctionelle stereotaxique de telencephale. In Talaraich, J. (ed.), *Atlas Stereotaxique de Telencephale*. Masson et cie, Paris, pp. 251–318.

Cambier, J. & Dehen, H. (1977) Imitation synkinesia and sensory control of movement. *Neurology*, **27**, 646–649.

Chiang, C.Y. & Lu, C.S. (1990) Delayed-onset posthemiplegic dystonia and imitation synkinesia. *J. Neurology, Neurosurgery Psychiatry*, **53**, 623.

Colebatch, J. G., Deiber, M. P., Passingham, R. E., Friston, K. J. & Frackowiak, R. S. (1991) Regional cerebral blood flow during voluntary arm and hand movements in human subjects. *J. Neurophysiol.*, **65,** 1392–1401.

Disbrow, E., Roberts, T. & Krubitzer, L. (2000) Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: evidence for SII and PV. *J. Comp. Neurol.*, **418**, 1–21.

Donchin, O., Gribova, A., Steinberg, O., Bergman, H. & Vaadia, E. (1998) Primary motor cortex is involved in bimanual coordination. *Nature*, **395**, 274–278.

Dow, R.S. (1987) Cerebellum, pathology: symptoms and signs. In Adelman, G. (ed.), *Encyclopedia of Neuroscience*. Birkhäuser, Boston, pp. 203–206.

Dum, R.P. & Strick, P.L. (1996) Spinal cord terminations of the medial wall motor areas in macaque monkeys. *J. Neurosci.*, **16**, 6513–6525.

Ehrsson, H.H., Fagergren, A., Jonsson, T., Westling, G., Johansson, R.S. & Forssberg, H. (2000) Cortical activity in precision versus power grip tasks: an fMRI study. *J. Neurophysiol.*, **83**, 528–536.

Ehrsson, H.H., Naito, E., Geyer, S., Zilles, K., Gulyas, B., Forssberg, H. & Roland, P.E. (1999) Somatotopic mapping of the human motor cortices: an fMRI study. *Soc. Neurosci. Abstr.*, **25**, 1408.

Fink, G.R., Frackowiak, R.S., Pietrzyk, U. & Passingham, R.E. (1997) Multiple nonprimary motor areas in the human cortex. *J. Neurophysiol.*, **77**, 2164–2174.

Fink, G.R., Marshall, J.C., Halligan, P.W., Frith, C.D., Driver, J., Frackowiak, R.S. & Dolan, R.J. (1999) The neural consequences of conflict between intention and the senses. *Brain*, **122**, 497–512.

Freund, H.-J. (1990) Premotor area and preparation of movement. *Revue Neurologique*, **10**, 543–547.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.B., Heather, J.D. & Frackowiak, R.S.J. (1995a) Spatial registration and normalization of images. *Human Brain Mapp.*, **2**, 165–189.

Friston, K.J., Frith, C.D., Liddle, P.F. & Frackowiak, R.S. (1993) Functional connectivity: the principal-component analysis of large (PET) data sets. *J. Cerebral Blood Flow Metab.*, **13,** 5–14.

Friston, K. J., Holms, A., Worsley, K. J., Poline, J. B., Frith, C. D. & Frackowiak, R. J. (1995b) Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapp.*, **2,** 189–210.

Friston, K.J., Worsley, K.J., Frackowiak, R.S.J., Mazziotta, J.C. & Evans, A.C. (1994) Assessing the significance of focal activations using their spatial extent. *Human Brain Mapp.*, **1**, 210–220.

Galea, M.P. & Darian-Smith, I. (1994) Multiple corticospinal neuron populations in the macaque monkey are specified by their unique cortical origins, spinal terminations, and connections. *Cerebral Cortex*, **4**, 166–194.

Gentilucci, M., Fogassi, L., Luppino, G., Matelli, M., Camarda, R. & Rizzolatti, G. (1988) Functional organization of inferior area 6 in the macaque monkey. I. Somatotopy and the control of proximal movements. *Exp. Brain Res.*, **71**, 475–490.

Geyer, S., Ledberg, A., Schleicher, A., Kinomura, S., Schormann, T., Burgel, U., Klingberg, T., Larsson, J., Zilles, K. & Roland, P.E. (1996) Two different areas within the primary motor cortex of man. *Nature*, **382**, 805–807.

Geyer, S., Schleicher, A. & Zilles, K. (1999) Areas 3a, 3b, and 1 of human primary somatosensory cortex. 1 Microstructural organization and interindividual variability. *Neuroimage*, **10**, 63–83.

Ghosh, S., Brinkman, C. & Porter, R. (1987) A quantitative study of the distribution of neurons projecting to the precentral motor cortex in the monkey. *J. Comp. Neurol.*, **259**, 424–444.

Grafton, S.T., Woods, R.P. & Mazziotta, J.C. (1993) Within-arm somatotopy

in human motor areas determined by positron emission tomography imaging of cerebral blood flow. *Exp. Brain Res.*, **95**, 172–176.
Grafton, S.T., Woods, R.P., Mazziotta, J.C. & Phelps, M.E. (1991) Somatotopic mapping of the primary motor cortex in humans: activation studies with cerebral blood flow and positron emission tomography. *J. Neurophysiol.*, **66**, 735–743.
He, S.Q., Dum, R.P. & Strick, P.L. (1993) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. *J. Neurosci.*, **13**, 952–980.
He, S.Q., Dum, R.P. & Strick, P.L. (1995) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere. *J. Neurosci.*, **15**, 3284–3306.
Kelso, J.A., Southard, D.L. & Goodman, D. (1979) On the coordination of two-handed movements. *J. Exp Psychology: Human Perception Performance*, **5**, 229–238.
Kleinschmidt, A., Nitschke, M.F. & Frahm, J. (1997) Somatotopy in the human motor cortex hand area. A high-resolution functional MRI study. *Eur. J. Neurosci.*, **9**, 2178–2186.
Kleist, K. (1907) Corticale (innervatorische) apraxie. *Jahrb. Psychiatrie Neurologie*, **28**, 46–112.
Kurata, K. (1989) Distribution of neurons with set- and movement-related activity before hand and foot movements in the premotor cortex of rhesus monkeys. *Exp. Brain Res.*, **77**, 245–256.
Larsson, J., Amunts, K., Gulyas, B., Malikovic, A., Zilles, K. & Roland, P.E. (1999) Neural correlates of real and illusory contour perception: functional anatomy with PET. *Eur. J. Neurosci.*, **11**, 4024–4036.
Lashley, K.S. (1930) Basic neuronal mechanisms in behaviour. *Psych. Rev.*, **37**, 1–24.
Ledberg, A. (2000) Robust estimation of the probabilities of 3D clusters in functional brain images: an application to PET data. *Human Brain Mapp.*, **9**, 143–155.
Ledberg, A., Akerman, S. & Roland, P.E. (1998) Estimation of the probabilities of 3D clusters in functional brain images. *Neuroimage*, **8**, 113–128.
Ledberg, A., O'Sullivan, B.T., Kinomura, S. & Roland, P.E. (1995) Somatosensory activations of the parietal operculum of man. A PET study. *Eur. J. Neurosci.*, **7,** 1934–1941.
Luria, A.R. (1966) *Higher Cortical Functions in Man*. Basic Books, New York.
Miller, S., Reitsma, D.J. & Van Der Meche, F.G.A. (1973) Functional organization of long ascending propriospinal pathways linking lumbo-sacral and cervical segments in the cat. *Brain Res.*, **62**, 169–188.
Miller, S., Van Der Burg, J. & Van Der Meche, F.G.A. (1975) Coordination of movements of the hindlimb and forelimb in different forms of locomotion in normal and decerebrate cats. *Exp. Brain Res.*, **91**, 217–237.
Mitz, A.R. & Wise, S.P. (1987) The somatotopic organization of the supplementary motor area: intracortical microstimulation mapping. *J. Neurosci.*, **7**, 1010–1021.
Muakkassa, K.F. & Strick, P.L. (1979) Frontal lobe inputs to primate motor cortex: evidence for four somatotopically organized 'premotor' areas. *Brain Res.*, **177**, 176–182.
Naito, E., Ehrsson, H.H., Geyer, S., Zilles, K. & Roland, P.E. (1999) Illusory arm movements activate cortical motor areas: a positron emission tomography study. *J. Neurosci.*, **19**, 6134–6144.
Nashner, L.M. & Grimm, R.G. (1978) Analysis of multiloop dyscontrols in standing cerebellar patients. *Prog. Clin. Neurophysiol.*, **5,** 300–309.
Nitschke, M. F., Kleinschmidt, A., Wessel, K. & Frahm, J. (1996) Somatotopic motor representation in the human anterior cerebellum. A high-resolution functional MRI study. *Brain*, **119,** 1023–1029.
Oldfield, R.C. (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, **9**, 97–113.
Ono, M., Kubik, S. & Abernathey, C.D. (1990) *Atlas of Cerebral Sulci*. Thieme Medical Publishers, New York.
Passingham, R.E. (1993) *The Frontal Lobes and Voluntary Action*. Oxford University Press, Oxford.
Passingham, R.E. (1996) Attention to action. *Philosoph. Trans. Roy. Soc. Lond. B: Biol. Sci.*, **351**, 1473–1479.
Penfield, W. & Boldrey, E. (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, **15**, 389–443.
Picard, N. & Strick, P.L. (1996) Motor areas of the medial wall: a review of their location and functional activation. *Cerebral Cortex*, **6**, 342–353.
Preuss, T.M. & Goldman-Rakic, P.S. (1989) Connections of the ventral granular frontal cortex of macaques with perisylvian premotor and somatosensory areas: anatomical evidence for somatic representation in primate frontal association cortex. *J. Comp. Neurol.*, **282**, 293–316.
Price, C.J., Moore, C. & Friston, K.J. (1997) Subtractions, conjunctions, and interactions in experimental design of activation studies. *Human Brain Mapp.*, **5**, 264–272.
Rees, G., Frith, C.D. & Lavie, N. (1997) Modulating irrelevant motion perception by varying attentional load in an unrelated task. *Science*, **278**, 1616–1619.
Rijntjes, M., Dettmers, C., Buchel, C., Kiebel, S., Frackowiak, R.S.J. & Weiller, C. (1999) A blueprint for movement: functional and anatomical representations in the human motor system. *J. Neurosci.*, **19**, 8043–8048.
Rizzolatti, G., Luppino, G. & Matelli, M. (1998) The organization of the cortical motor system: new concepts. *Electroencephalogr. Clin. Neurophysiol.*, **106**, 283–296.
Robinson, C.J. & Burton, H. (1980a) Organization of somatosensory receptive fields in cortical areas 7b, retroinsula, postauditory and granular insula of M. fascicularis. *J. Comp. Neurol.*, **192**, 69–92.
Robinson, C.J. & Burton, H. (1980b) Somatotopographic organization in the second somatosensory area of M. fascicularis. *J. Comp. Neurol.*, **192**, 43–67.
Roland, P.E., Geyer, S., Amunts, K., Schormann, T., Schleicher, A., Malikovic, A. & Zilles, K. (1997) Cytoarchitectural maps of the human brain in standard anatomical space. *Human Brain Mapp.*, **5**, 222–227.
Roland, P.E., Graufelds, C., Wåhlin, J., Ingelman, L., Andersson, M., Ledberg, A., Pedersen, J., Åkerman, S., Dabringhaus, A. & Zilles, K. (1994) Human brain atlas: for high resolution functional and anatomical mapping. *Human Brain Mapp.*, **2**, 1–12.
Roland, P.E., Larsen, B., Lassen, N.A. & Skinhoj, E. (1980) Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J. Neurophysiol.*, **43**, 118–136.
Roland, P.E. & Zilles, K. (1996) Functions and structures of the motor cortices in humans. *Current Opin. Neurobiol.*, **6**, 773–781.
Roland, P.E. & Zilles, K. (1998) Structural divisions and functional fields in the human cerebral cortex. *Brain Res. Brain Res. Reviews*, **26**, 87–105.
Rouiller, E.M., Babalian, A., Kazennikov, O., Moret, V., Yu, X.H. & Wiesendanger, M. (1994) Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. *Exp. Brain Res.*, **102**, 227–243.
Sadato, N., Ibanez, V., Campbell, G., Deiber, M.P., Le, B.D. & Hallett, M. (1997b) Frequency-dependent changes of regional cerebral blood flow during finger movements: functional MRI compared to PET. *J. Cereb. Blood Flow Metab.*, **17**, 670–679.
Sadato, N., Yonekura, Y., Waki, A., Yamada, H. & Ishii, Y. (1997a) Role of the supplementary motor area and the right premotor cortex in the coordination of bimanual finger movements. *J. Neurosci.*, **17**, 9667–9674.
Schleicher, A., Amunts, K., Geyer, S., Morosan, P. & Zilles, K. (1999) Observer-independent method for microstructural parcellation of cerebral cortex: a quantitative approach to cytoarchitectonics. *Neuroimage*, **9,** 165–177.
Shinoda, Y., Zarzecki, P. & Asanuma, H. (1979) Spinal branching of pyramidal tract neurons in the monkey. *Exp. Brain Res.*, **34**, 59–72.
Stephan, K. M., Binkofski, F., Halsband, U., Dohle, C., Wunderlich, Schnitzler, A., Tass, P., Posse, S., Herzog, H., Sturm, V., Zilles, K., Seitz, R. J. & Freund, H. J. (1999) The role of ventral medial wall motor areas in bimanual co-ordination. A combined lesion and activation study. *Brain*, **122,** 351–368.
Stepniewska, I., Preuss, T.M. & Kaas, J.H. (1993) Architectonics, somatotopic organization, and ipsilateral cortical connections of the primary motor area (M1) of owl monkeys. *J. Comp. Neurol.*, **330**, 238–271.
Swinnen, S.P., Jardin, K., Meulenbroek, R., Dounskaia, N. & Hofkens-Van Den Brandt, M. (1997) Egocentric and allocentric constraints in the expression of patterns of interlimb coordination. *J. Cognitive Neuroscience*, **9**, 348–377.
Talaraich, J. & Tournoux, P. (1988) *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme, Stuttgart.
Tanji, J., Okano, K. & Sato, K.C. (1987) Relation of neurons in the nonprimary motor cortex to bilateral hand movement. *Nature*, **327**, 618–620.
Thach, W.T., Goodkin, H.P. & Keating, J.G. (1992) The cerebellum and the adaptive coordination of movement. *Annu. Rev. Neuroscience*, **15**, 403–442.
Tokuno, H. & Tanji, J. (1993) Input organization of distal and proximal forelimb areas in the monkey primary motor cortex: a retrograde double labeling study. *J. Comp. Neurol.*, **333**, 199–209.
Weinhard, K., Dahlbom, M., Eriksson, L., Michel, C., Bruckbauer, T., Pietrzyk, U. & Heiss, W.D. (1994) The ECAT EXACT HR: performance of a new high resolution positron scanner. *J. Computer Assisted Tomogr.*, **18**, 110–118.
Woods, B.T. & Teuber, H.L. (1978) Mirror movements after childhood hemiparesis. *Neurology*, **28**, 1152–1157.