The role of ventral medial wall motor areas in bimanual co-ordination

A combined lesion and activation study

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Summary

Two patients with midline tumours and disturbances of bimanual co-ordination as the presenting symptoms were examined. Both reported difficulties whenever the two hands had to act together simultaneously, whereas they had no problems with unimanual dexterity or the use of both hands sequentially. In the first patient the lesion was confined to the cingulate gyrus; in the second it also invaded the corpus callosum and the supplementary motor area. Kinematic analysis of bimanual in-phase and anti-phase movements revealed an impairment of both the temporal adjustment between the hands and the independence of movements between the two hands. A functional imaging study in six volunteers, who performed the same bimanual in-phase and anti-phase tasks, showed strong activations of midline areas including the cingulate and ventral supplementary motor area. The prominent activation of the ventral medial wall motor areas in the volunteers in conjunction with the bimanual co-ordination disorder in the two patients with lesions compromising their function is evidence for their pivotal role in bimanual co-ordination.

Keywords: medial wall motor areas; cingulate motor areas; supplementary motor area; bimanual interaction; neuroimaging

Abbreviations: FFT = fast Fourier transform; fMRI = functional MRI; rCBF = regional cerebral blood flow; SMA = supplementary motor area; SPM = statistical parametric mapping

Introduction

Bimanual co-ordination relies on two main factors: independence of hand movements between the two sides and the synergy of the two hands in common actions. Damage of the precentral motor strip or its descending fibres interferes with contralateral and sometimes, to a minor degree, with ipsilateral hand function (Jebsen *et al*., 1971; Colebatch and Gandevia, 1989). Bimanual activities are disturbed accordingly. Specific disturbances of bimanual motor acts have been described after lesions of midline structures with and without callosal damage (Laplane *et al*., 1977; Zaidel and Sperry, 1977; Geffen *et al*., 1994). Irrespective of their more anterior or posterior location, a wide spectrum of disturbances (mirror movements, alien hand syndrome, callosal dyspraxia) has been described. In most cases one hand is out of the patient's volitional control. The allocation of this involuntary motor behaviour to a particular midline structure has not been possible due to the wide scatter in the size and site of the lesions.

The functional significance of the medial frontal cortex for bilateral movements is further supported by anatomical, electrophysiological and lesion data in the monkey. Anatomically, there are strong interhemispheric connections between the two supplementary motor areas (SMA), including distal representations of the arm and hand (Rouiller *et al*., 1994) and strong bilateral SMA projections to the basal ganglia. Neuronal activity within the SMA was associated both with contralateral and ipsilateral arm movements (Brinkman and Porter, 1979; Tanji *et al*., 1988). Bimanual movement sequences were impaired by lesions in the frontomedial cortex, including the SMA and anterior cingulate (e.g. Travis, 1955; Brinkman, 1984). Kinematic analysis of the effect of well defined lesions of the SMA showed increased variability in the performance of either hand during bimanual tasks, but surprising stability and precision of the final interaction of the two hands at the target (Kazennikov *et al*., 1994; Wiesendanger *et al*., 1996). This preservation of 'goal invariance' in conjunction with neuronal recording data led the authors to conclude that the SMA is clearly engaged in bimanual tasks, but possibly does not represent the bimanual command structure.

Functional activation studies have shown that the SMA is involved in many aspects of sensorimotor functions, including ideation and the planning, initiation and performance of motor tasks (for review, see Picard and Strick, 1996). Experimental data have allocated the more complex aspects of motor behaviour to more anterior parts of the SMA, including the pre-SMA, and the more executive processes of motor behaviour to the SMA proper (Stephan *et al*., 1995; Grafton *et al*., 1996; Passingham, 1996). Recently, differential activations have also been reported for the cingulate motor areas in various motor tasks (Picard and Strick, 1996; Fink *et al*., 1997). Dettmers *et al*. (1995) have shown that areas at the opening and in the depths of the cingulate sulcus—but not in the SMA proper—show a positive correlation between regional cerebral blood flow (rCBF) and force levels, suggesting a close association of the cingulate motor areas with the actual performance of a motor task.

In this article we describe two patients with ventral midline tumours. They had difficulties whenever the two hands had to act together, but no problems in using the two hands sequentially or either hand independently. In one patient the tumour was restricted to the central part of the cingulate gyrus, extending from 10 mm anterior to 30 mm posterior to the AC line, without affecting the SMA or corpus callosum, whereas the other patient's lesion involved all three areas. Complementary functional activation studies conducted in six normal subjects showed strong activation of the ventral medial wall motor areas during bimanual actions. Along with the bimanual co-ordination disorder in the two patients, this is compatible with a prominent role of the ventral medial wall motor areas in bimanual interaction.

Method

Patients and normal controls

Clinical data

Patient I.M. This patient was a 62-year-old right-handed woman. She had noticed a mild tremor of the left hand and leg for the past 4 years. There was no family history of tremor. Her main complaint, however, was a specific disturbance of everyday bimanual motor acts. She reported that she could engage either hand in a skilful way, but as soon as bimanual interaction was required motor behaviour was unco-ordinated.

Formal neurological examination showed a slight resting and action tremor (6–7 Hz) of the left limbs. After performing fast repetitive movements of her left arm or leg, she sometimes developed intermittent dystonia of her left hand and foot. Fractionated finger movements of her left hand were marginally impaired, even though formal force testing was completely normal (maximal grip force: right, 0.9 bar; left, 1.0 bar). Tendon reflexes were normal. Pyramidal signs were absent. She showed slight dysdiadochokinesia of her left hand. During walking her steps were shorter on the left side. The major finding was the inco-ordination between the two arms and the two hands, so that bibrachial or bimanual rotations could not be correctly performed. Daily bimanual activities such as tying shoelaces, buttoning, etc. were severely disordered.

A computerized test battery for elementary motor function (Motorische Leistungs Serie, MLS) (Sturm and Büsing, 1995) showed that unimanual movements of her left hand were slower than those of her right hand during both the tapping and the peg-insertion task (Table 1).

Neuropsychological testing showed an average verbal IQ (107; MWT-B—Mehrfach-Wortschatz-Test-Form B), normal results for memory and attention in a test battery (SKT—Syndromkurztest) and average performance on a reaction time task (Wiener Determinationsgerät), with improvement over successive learning trials. She had full visual fields without any signs of visual neglect (Albert's test, line-bisection test).

Patient G.A. This patient was a 39-year-old right-handed man. He complained of weekly focal motor seizures of his right hand during the last 6 weeks before admission. He had noticed that he could not tap a rhythm bimanually while playing with his children because both hands were always out of phase. Additionally, he could not shake a milk bottle for his children with one hand while keeping it closed with the other hand.

On formal neurological examination he showed a slight dysdiadochokinesia and dysmetria and a marginal impairment of fine finger movements of his left hand. Furthermore, alternating rotating movements of the arms or cycling movements of the legs were not co-ordinated. Unlike patient I.M., he had no difficulty in bimanual movements such as tying his shoelaces and manipulating his shirt buttons. Force (maximal grip force right and left, 0.9 bar), tone and reflexes were normal and the Babinski sign was negative. Sensory functions were normal.

The results of the computerized test battery for elementary motor performance showed normal results for unimanual and bimanual tapping (Table 1). However, peg insertion was clearly disturbed on the left side (Table 1).

Neuropsychological testing showed a verbal IQ above average (124; MWT-B). He was not impaired on memory and attention tasks (SKT). Cognitive flexibility was within normal range (e.g. trail-making test, part B), and there were no difficulties in rhythm discrimination under normal and delayed conditions. He had full visual fields without any signs of visual neglect (Albert's test, line-bisection test).

For seizure control, he was on 1600 mg carbamazepine per day.

Table 1 *Motor performance in two patients*

	Patient I.M.		Patient G.A.	
	Right hand	Left hand	Right hand	Left hand
Unimanual tapping (*n*/30 s)	178	131	189	181
Bimanual tapping (*n*/30 s)	143	171*	134	133
25 unimanual peg insertions (s)	46.48	65.62	54.28	75.66
25 bimanual peg insertions (s)	98.08	97.41	81.62	100.13

Results of a computerized test-battery for motor performance (Motorische Leistungs Serie). Unimanual and bimanual tapping rate in 30 s for both patients for right and left hands separately. Duration (s) of insertion of 25 pegs (40 mm long) into specially drilled holes at a distance of up to 30 cm again during uni- and bimanual performance. *Including double contacts due to slight tremor.

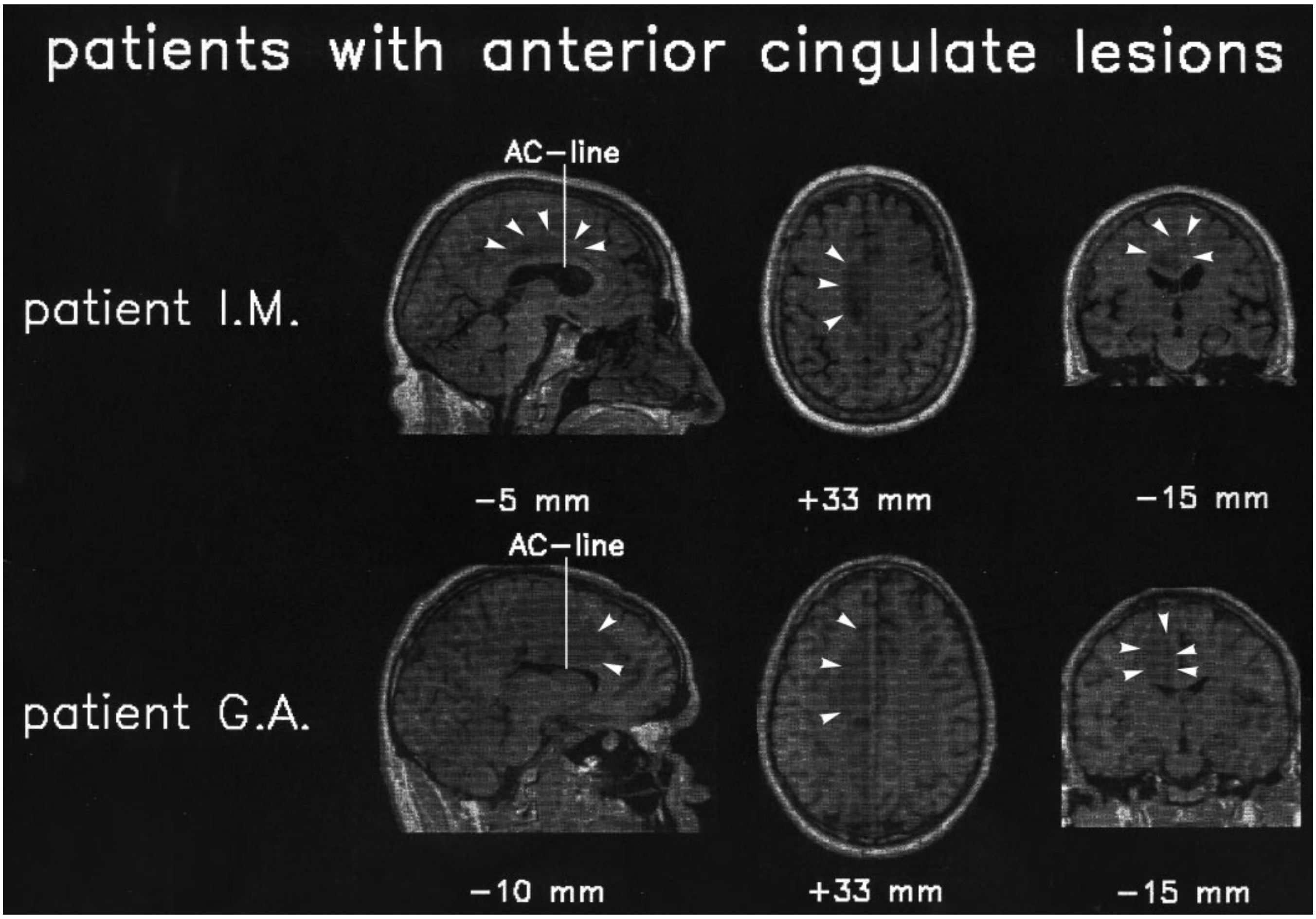


Fig. 1 Sagittal slices of MRIs through right anterior cingulate of the two patients. The slices are 5 mm (patient I.M.) and 10 mm (patient G.A.) to the right of the sagittal midline. In patient I.M. there is clear involvement of the ventral medial wall without invasion of the corpus callosum or supplementary motor area (arrows). There is hardly any oedema. In all other slices, the lesion was also confined to the right anterior cingulate. In patient G.A. the tumour invades both the ventral medial wall and the corpus callosum (arrows). The oedema extends into the lower parts of the right supplementary motor area.

Structural imaging and histology

Patient I.M. showed a solid lesion confined to the central part of the right cingulate gyrus (Fig. 1, upper part). The lesion was located in the lower part of the cingulate gyrus directly above the corpus callosum, which was spared. On sections vertical to the intercommissural line it extended from ~10 mm anterior to 30 mm posterior to the AC line. T_1 MRI showed a hypointense lesion with sharp borders and no gadolinium enhancement. T_2-weighted images showed a hyperintense area without signs of infiltration or oedema into either the corpus callosum or the SMA. A stereotaxic biopsy was performed after the study, and yielded the typical histology of a grade II astrocytoma.

In patient G.A. the MRI showed damage of the right cingulate gyrus and the adjacent corpus callosum (Fig. 1, lower part). It extended from ~20 mm anterior to the AC line 60 mm posteriorly to the front of the marginal part of the cingulate sulcus. In T_1-weighted images the lesion was inhomogeneous. A posterior part appeared to infiltrate the isthmus of the corpus callosum, and a more anterior component was located mainly within the lower part of the cingulate cortex directly above the corpus callosum and below the cingulate sulcus. T_2-weighted images showed perifocal oedema of the adjacent anterolateral white matter area extending up to the superior frontal sulcus and mesiofrontal areas above the cingulate gyrus, including the SMA. Histology of a stereotaxic biopsy, again performed after PET scanning, showed a grade III astrocytoma.

Normal subjects

We investigated as controls six healthy subjects (mean age, 32 years) without a history or signs of a neurological or psychiatric illness. None of them showed any structural lesion on cranial MRI. Right-handedness was assessed by the Edinburgh Inventory (Oldfield, 1971). The study was approved by the local ethical committee of the Heinrich-Heine-University, and all subjects gave informed consent.

Kinematic and functional imaging data

The task

Normal subjects and patients performed four different sets of movements: unimanual index finger–thumb opposition movements with the right hand (A), the same movements with the left hand (B), bimanual finger–thumb opposition movements with both hands in-phase (C) and with both hands anti-phase (D). Movements were self-paced to allow every subject to find his preferred frequency during each of the four tasks and to allow us to compare kinematic characteristics between subjects and patients. The kinematic data of the patients reflected exactly the performance during the scans as they were recorded during PET scanning. For normal subjects there was, however, a difference between the tasks inside and outside the MRI scanner. During the functional imaging session subjects were first externally paced before performance of the task at 1 Hz in order to avoid a systematic influence of the degree of activation due to the different movement rates. Results of the kinematic recordings in normal subjects obtained outside the MRI scanner are therefore not identical to their actual movements during the scans.

Kinematic recordings

Movements were monitored using two twin-axis goniometers (Penny & Giles, Blackwood Ltd, Blackwood, Gwent, UK) to measure the angle between index finger and thumb. Analogue signals of the goniometers were amplified by two preamplifiers adjusted to a range from 0 to 5 V. Then signals were digitized at 100 Hz for 90 s by means of an analogue–digital converter [CED2000, Cambridge Electronics Design (CED), Cambridge, UK] using the software package Spike 2 [Cambridge Electronics Design (CED), Cambridge, UK]. Kinematic analysis was performed with MATLAB programming tools (The Mathworks Inc., Natick, Mass., USA). Signals were filtered by a dual-pass filter with a cut-off frequency of 10 Hz. Correlation coefficients between right and left signals and the fast Fourier transforms (FFTs) of each signal were calculated for periods of 90 s after movement onset. Peak frequency was determined as the maximum of the power spectrum in the range 0.25–10.25 Hz. For bimanual movements the relative phase between the movements of the two hands was calculated. The time history of the right hand was taken as reference, so that the difference between the maxima of the two sinusoid curves was expressed as part of the instantaneous phase relationship. Negative values (–0.5 to 0) corresponded to an advanced left hand, positive values (0 to 0.5) to a right-hand advance.

fMRI scanning in normal subjects

Functional MRI (fMRI) data were obtained with a Siemens Vision system (1.5 T). Echoplanar sequences [TR (repetition time), 3 s; TE (echo time), 66 ms; α (flip angle), 90°] with the BOLD (blood oxygenation level dependence) effect were used. Ten consecutive slices of 4 mm thickness adjusted to the AC–PC (anterior–posterior commissure) line and positioned above the corpus callosum were acquired. Voxel size was $3 \times 3 \times 4$ mm. Five periods of 15 s rest were each followed by a period of 15 s activation.

Successive functional imaging data were realigned for movement correction [Statistical Parametric Mapping Program, 1996 (SPM '96), Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; Friston *et al*., 1995*a*, *b*]. After coregistration of the data sets with the individual structural MRIs, the realigned data were transformed into Talairach space (Talairach and Tournoux, 1988) as defined by the standard brain of the Montreal Neurological Institute, Canada, which is provided by SPM '96. After smoothing with a filter of 8 mm width, task–rest comparisons were calculated and statistical analysis was performed for all four conditions compared with rest in the individual subjects, using a significance level (height threshold) of $P < 0.0005$ and an additional extent threshold of $P < 0.05$ (SPM '96; Friston *et al*., 1994, 1995*a*, *b*). Comparisons between conditions (anti-phase and in-phase) were additionally performed in predefined areas (primary somatosensory areas, mesial premotor areas including SMA and anterior cingulate, and dorsolateral premotor areas) at a significance level of $P < 0.01$. Statistically significant areas were superimposed on individual brain anatomy in Talairach space using the MPI Tool (v1.01; Multiple Purpose Imaging Tool, Max-Planck-Institut für Neurologische Forschung, Cologne, Germany) and SPM routines.

PET scanning in patients

In the two patients the four 'active' tasks were compared with a control condition, where patients were lying still without any voluntary finger movement. The patient's head was stabilized with an individual moulded head support. The patient was asked not to perform any other movements, including eye movements, during PET scanning, not to count internally and to keep the eyes closed.

The rCBF was measured for a period of 40 s after intravenous injection of [^{15}O]butanol as radioactive tracer (~40 mCi per scan). Bolus injections were performed into the right brachial vein and were immediately flushed with 10 ml saline. Prior to emission scans, a transmission scan was obtained for attenuation correction using a rotating ^{68}Ge pin source. Dynamic changes in brain activity were measured by sequential recordings of brain activity in frames of 2 s duration (list mode). The eight-ring PET camera (Scanditronix PC 4096–15WB) had an optimal spatial resolution of 4.6 mm in plane, and a slice distance of 6.5 mm (Rota Kops *et al*., 1990). The 15 PET image slices were reconstructed with a Hanning filter to an effective image resolution (full width half maximum) of 9.0 mm.

Subtraction images were calculated on a pixel-by-pixel basis from 15 sequential images, and pixels exhibiting significant activations were determined after thresholding at a t value of 2.947 ($P < 0.01$ uncorrected). As determined previously, significant areas of activation ($P < 0.01$ corrected for image resolution and multiple comparisons) had to exceed clusters of 16 suprathreshold pixels (Wunderlich *et al*., 1997). The anatomical location of significant rCBF changes was determined by coregistration of the mean PET scans with the subjects' individual MRIs using a spatial alignment algorithm (Steinmetz *et al*., 1992).

Neuropsychological and electrophysiological testing of the patients

Imitation of pantomimed motor acts

The two patients were presented with 50 meaningful pantomimed motor acts on a video screen and were asked to imitate the motor acts from memory with their ipsilateral or contralateral hand (unimanual conditions) or with both hands simultaneously (bimanual condition).

Unimanual motor tasks included ten symbolic and conventional gestures, such as waving, saluting and threatening, ten pantomimed actions aimed at producing explicitly defined movements towards parts of the subject's own body (e.g. combing one's hair or brushing one's teeth), and ten pantomimed imitations of motor acts with respect to the location of an imagined recipient of a tool's action in extrapersonal space (e.g. hammering a nail into a wall, pouring water into a glass or using a screwdriver). Patients used the ipsi- and contralesional hand in a randomized order across trials. Performance on all production tests was videotaped and scored independently by two examiners as correct or incorrect.

In the bimanual condition, subjects were requested to imitate 20 meaningful movements using both hands simultaneously. Half of the actions presented consisted of two homogeneous components whereby both hands performed an identical movement with respect to an imagined object, such as wringing out wet clothes or piano-playing with symmetrical finger movements. The other ten actions consisted of heterogeneous movement patterns such as pouring pudding powder into boiling milk with their left hand while simultaneously stirring it with the right hand.

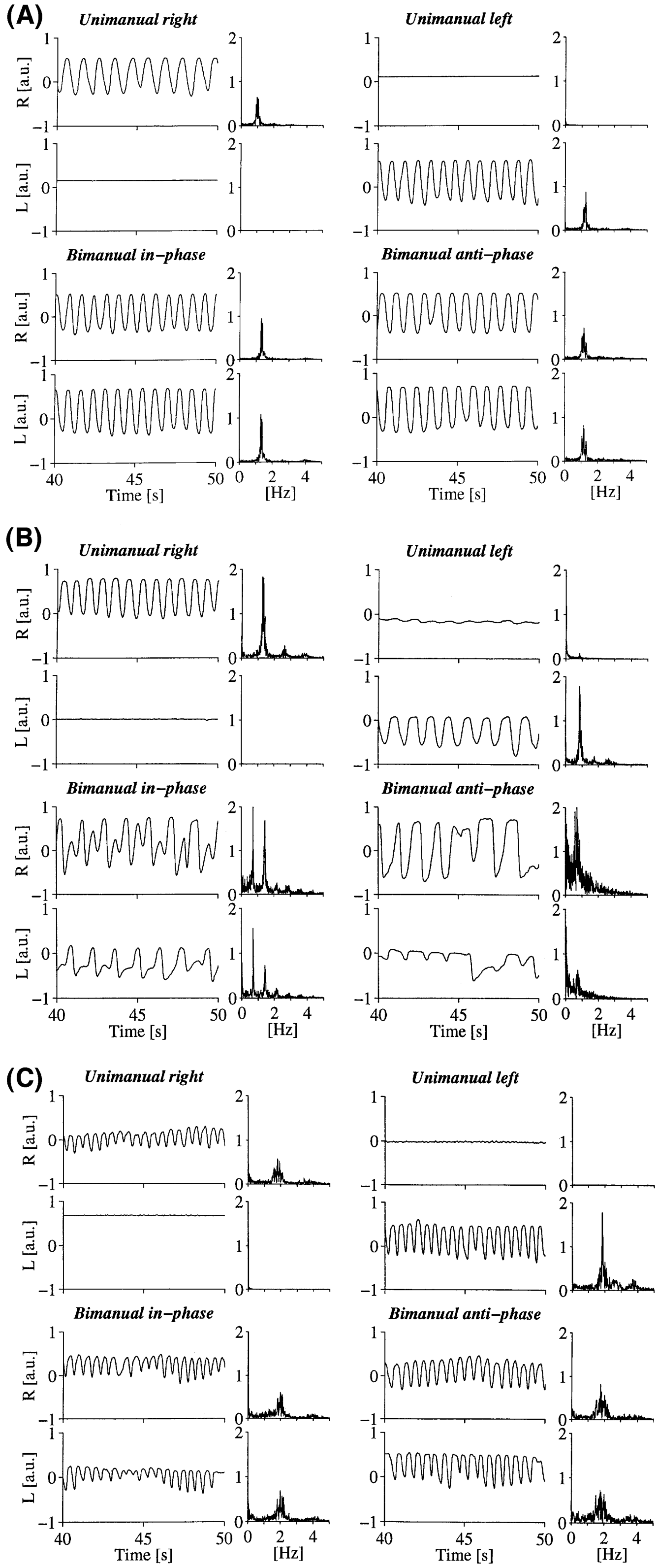
Sensory conditional learning tasks: motor versus spatial selection

This test procedure was described by Halsband and Freund (1990). In short, at first patients were asked to discriminate six different visual stimuli (coloured plates): they had to judge whether two successive stimuli were identical or not. Thereafter they learned to assume six different postures with their right dominant arm and hand, which were presented by the examiner. In the next stage each of the visual stimuli had to be associated with one (and only one) of the hand postures that had been rehearsed previously. The task was to find out by trial and error which movement was the correct one for each stimulus. After each response the patient was informed whether the correct movement had been performed. Testing continued until the patient had learned the task (18 correct responses on 18 consecutive trials) or up to a maximum of 250 trials.

In a second experiment the same visual stimuli were used. This time, however, the subjects did not perform different arm movements but had to differentiate between circles on a board: six black circles were placed in an irregular array and the patient was instructed that the position of each circle was associated with one of the six visual stimuli. The task was to learn which spatial position was the correct one for each sensory stimulus. The patients responded by pointing to the appropriate circle associated with a given visual stimulus, and were thus pointing to different locations in space. Otherwise the procedure was the same as for the first experiment.

Transcranial magnetic stimulation

In both patients, transcallosally mediated effects between primary motor cortices were examined in order to test the integrity of transcallosal connections using the experimental paradigm described by Schnitzler *et al*. (1996). Transcranial magnetic stimulation was performed using two magnetic stimulators (Novametrix Magstim Company, Whitland, Dyfed, UK), each connected to a flat figure-of-eight coil. Magnetic test stimuli were given to the left-hand motor cortex and conditioning stimuli were delivered to the opposite motor cortex at different intervals (2, 5, 10, 15, 20, 50, 100 ms) prior to the test stimuli. The duration of the silent period in the right first dorsal interosseus muscle was determined for each conditioning–test-stimulus interval (for details, see



Schnitzler *et al.*, 1996). The data for the two patients were compared with those for a control group of eight healthy right-handed subjects. In this group of normal subjects with intact corpus callosum, silent period duration was significantly reduced at conditioning–test-stimulus intervals of 10–20 ms (Schnitzler *et al.*, 1996).

Results

Kinematic recordings

All normal subjects performed regular unimanual and bimanual index finger–thumb opposition movements, as reflected by sharp maxima in the FFT (Fig. 2A) and in the power spectra between 0.5 and 2 Hz depending on the rate preferred by the subject. Mean movement rates were similar for the right hand (0.95 Hz) and left hand (0.99 Hz) (Table 2).

During bimanual movements the maxima of the power spectra were similar for the two hands during in- and anti-phase movements (Fig. 2A, bottom row; Table 2). There were only minimal fluctuations of the relative phase between the two hands during in-phase movements (Fig. 3A) and a nearly constant half-cycle shift (0.5) between the two hands during anti-phase movements (Fig. 3B). Correlation analysis showed a higher degree of synchrony during in-phase movements (mean 0.979) than during anti-phase movements (mean –0.897) for all six subjects (test for differences between absolute values using the paired t test: $t < 0.001$).

In both patients unimanual movements of the left hand were disturbed. Patient I.M. performed regular movements with the right hand (Fig. 2B, top left). During unimanual movements with the left hand, performance was slower (Table 2) and small additional in-phase mirror movements of the right hand became apparent (Fig. 2B, top right). The

Fig. 2 Goniometer recordings and FFT spectra of right hand, left hand, bimanual in-phase and bimanual anti-phase index finger–thumb opposition movements in a normal subject (**A**), in patient I.M. (**B**) and in patient G.A. (**C**) at rates chosen by the subjects. Filtered goniometer recordings for 10 s and FFT spectra of movement-periods of 90 s are shown in the top rows for unimanual movements and in the bottom rows for bimanual movements. [Ordinate: amplitude in arbitrary units (a.u.)]. (**A**) The panels and the sharp spectral maxima show regular movements during all four conditions, with nearly perfect coupling between the two hands in the bimanual conditions. (**B**) Patient I.M. showed regular unimanual movements with the right hand (*top left*). During unimanual movements with the left hand, however, she performed small in-phase mirror movements with the right hand (*top right*). In-phase movements showed regular spectral peaks, but with marked variability of amplitude (*bottom left*). During anti-phase movements the movements of the two hands were repeatedly performed in-phase instead of anti-phase, resulting in spectral broadening (*bottom right*). (**C**) Patient G.A. performed regular uni- and bimanual movements with his right and left hands. In contrast to patient I.M., there were no associated movements of either right or left hand. FFT spectra were broader than in normal subjects, indicating that the frequency was less stable than in normal subjects.

Table 2 *Mean movement rates during thumb–index finger opposition movements*

	Right hand	Left hand	In-phase	Anti-phase
Normal subjects (n = 6): mean (SD)	0.95 (0.38)	0.99 (0.42)	1.02 : 1.02 (0.41 : 0.41)	0.82 : 0.83 (0.35 : 0.35)
Patient I.M.	1.25	0.84	0.72 : 0.72	0.71 : 0.71
Patient G.A.	1.79	1.83	1.99 : 1.99	1.76 : 1.76

Mean movement rates are given as maxima of power spectra (Hz) of filtered goniometer signals for periods of 90 s.

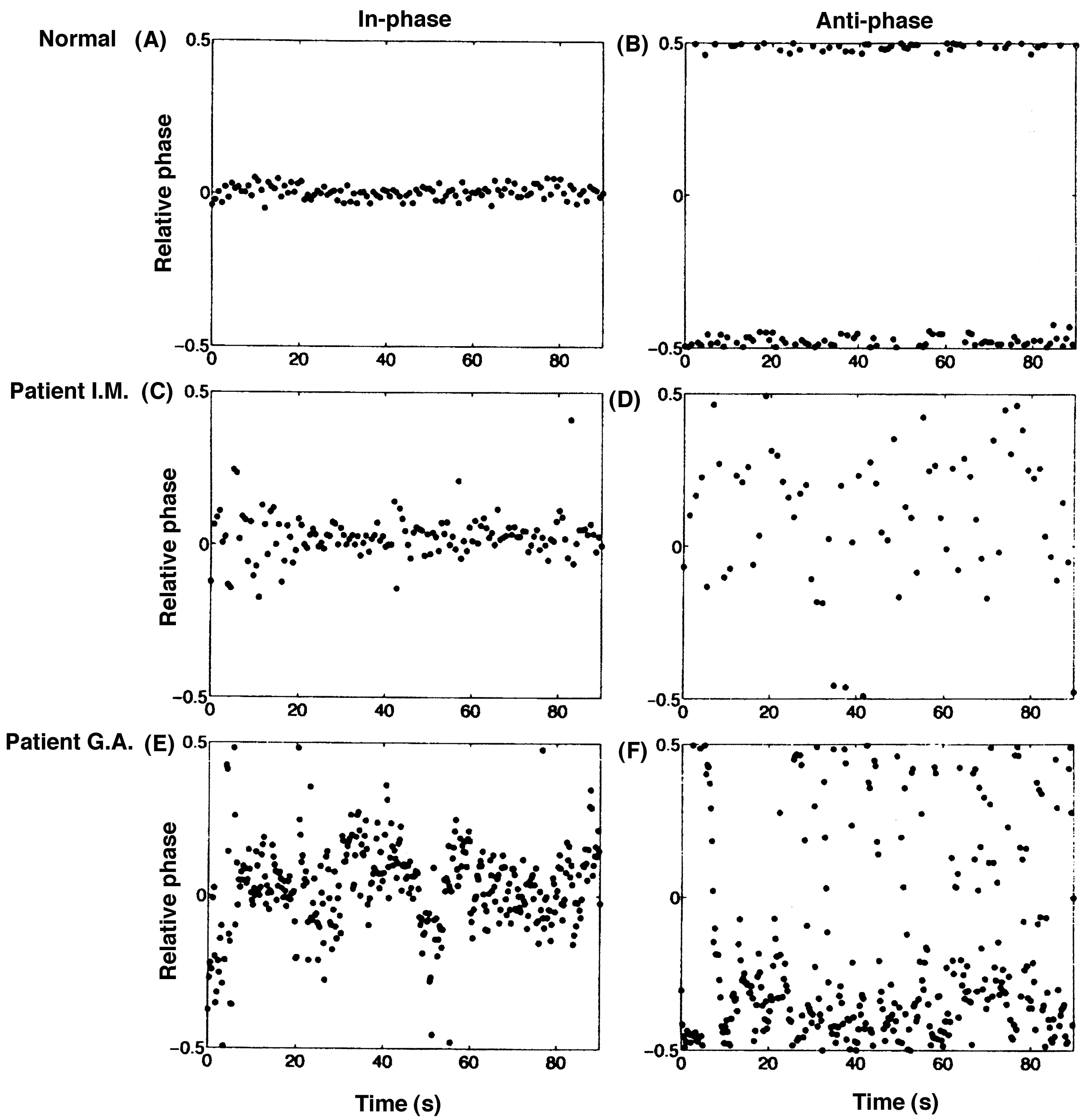


Fig. 3 Relative phase shifts between the different cycles in a normal subject (**A** and **B**), in patient I.M. (**C** and **D**) and in patient G.A. (**E** and **F**) for both in-phase and anti-phase bimanual movements. In the normal subject there are no or minor phase shifts in either condition between cycles (**A** and **B**). Patient I.M. shows only small phase shifts for the in-phase condition (**C**) but large phase shifts for the anti-phase task (**D**). For patient G.A. there are large phase shifts for both the in-phase and the anti-phase condition (**E** and **F**).

spectral peaks were the same for the two sides, but the amplitudes of the associated movements of the right hand were much smaller. Patient G.A. showed regular movements with clear frequency peaks during the unimanual tasks of the right and left hands in the present task (Fig. 2C, top row; Table 2). In contrast to patient I.M., there were no associated movements of the other hand, but rate variability was higher than in control subjects, leading to broader FFT maxima. The relative impairment of the left hand became obvious only during more complex tasks, such as during peg insertion (Table 1).

Bimanual movements were impaired in both patients: patient I.M. performed regular bimanual in-phase movements with large variation in amplitude. Relative phase-shifts were minimal except for some jitter. The range of jitter was larger than that of the normal subjects (compare Fig. 3C with Fig. 3A). However, as the amplitude of the movements varied considerably (Fig. 2B, bottom left), the correlation coefficient between right and left hand movements was low (0.107). During anti-phase movements, this patient tried unsuccessfully to co-ordinate her two hands: most of the time movements of the fingers of the two hands were not performed in opposite directions but in the same direction (Fig. 2B, bottom right). The relative phase varied markedly during the anti-phase task, so that the patient was not able to perform the anti-phase movement (Fig. 3D; correlation coefficient = 0.060). Patient G.A. performed bimanual movements regularly but not synchronously during both the in-phase and the anti-phase condition. As during unimanual movements, there were again broader FFT maxima than in normal controls (Fig. 2C, bottom row). Furthermore, G.A. showed a tendency towards an oscillatory pattern of the relative phase for both the in-phase and the anti-phase condition (Fig. 3E and F). This pattern was mainly located around 0 for the in-phase and around 0.4 for the anti-phase condition. Correlation analysis again showed a lesser degree of synchrony between the hands than in normal subjects for in-phase (correlation coefficient = 0.537) and anti-phase movements (correlation coefficient = –0.448).

Functional imaging data

Normal subjects

In each subject unimanual finger–thumb opposition tasks led to strong activation of the contralateral primary sensorimotor area ($P < 0.0005$ corrected for spatial extent $P < 0.05$). During right-hand and left-hand movements, the activated areas in two of the subjects for each condition included premotor areas in front of the precentral sulcus or close to the superior frontal sulcus of the contralateral hemisphere. Within the mesial frontal cortex the main focus of activation lay within or just above the left cingulate sulcus. In five of six subjects there was activation above the left cingulate sulcus during right-hand movements. During left-hand movements three subjects activated similar areas above the left (ipsilateral) cingulate sulcus and two above the right cingulate sulcus.

During bimanual movements both primary sensorimotor areas became active in all six subjects (e.g. Table 3). During the in-phase condition right dorsolateral premotor areas anterior to the precentral gyrus in front of the primary motor hand area or close to the superior frontal sulcus became active in one subject, and left dorsolateral premotor areas became active in another subject (Table 3). Two further subjects showed activity in the right dorsolateral premotor cortex during the anti-phase condition, and another patient showed activity in the left dorsolateral premotor cortex. Within the mesial frontal cortex, the site of maximal activity was again in the areas close to and just above the left cingulate sulcus. These areas became activated in four of the six subjects during the in-phase condition (Fig. 4, upper panel; Table 3) and in all six during the anti-phase condition (Fig. 4, middle panel; Table 3). However, the main difference between in-phase and anti-phase conditions was seen within the right mesial cortex: areas above the right cingulate sulcus were active in only two subjects during the in-phase condition but in five subjects during the anti-phase condition (Fig. 4; Table 3).

Areas above the paracingulate sulcus and within the mesial cortex above the paracingulate sulcus, which presumably form part of the SMA, became active in one subject during the in-phase condition and in two subjects during the anti-phase condition. However, we have to be cautious in commenting on the number of activations within the dorsal SMA, as the dorsal surface of the brain lay within the most dorsal slice obtained in four of the six subjects, and small activations in this area are therefore prone to artefacts.

The activations in the primary sensorimotor, dorsolateral premotor and mesial frontal cortex were also compared directly between the two bimanual conditions at the lower statistical threshold of $P < 0.01$. Results showed that within the mesial wall areas in-phase and anti-phase movements differed not only within the right hemisphere: in five of the six subjects there was also a significant increase in activation close to the left cingulate sulcus. In most of the subjects the peak of this activity was slightly rostral or caudal to the main activation during in-phase movements (e.g. Fig. 4, bottom panel), indicating that during the anti-phase task there is a wider scatter of activity within the left cingulate sulcus. The additional activity within the right dorsolateral premotor cortex in three subjects and within the right cingulate sulcus in another three subjects (e.g. Fig. 4) confirms the additional right-hemispheric activation during the anti-phase condition. Again, two subjects showed additional activity within or above the paracingulate sulci.

There was no prominent change in the primary sensorimotor areas: only one subject showed a significant difference for the right and one for the left hemisphere. The ventral prefrontal cortices, subcortical structures and cerebellum were outside the field of view of the 10 MRI slices.

Table 3 *Activation patterns during bimanual movements*

	In-phase movements			Anti-phase movements		
	Normal subjects	Patient I.M.	Patient G.A.	Normal subjects	Patient I.M.	Patient G.A.
Sensorimotor area (right hemisphere)	6/6	+	−	6/6	−	−
Sensorimotor area (left hemisphere)	6/6	+	+	6/6	+	+
Ventral medial wall (right hemisphere)	2/6	+	−	5/6	+	−
Ventral medial wall (left hemisphere)	4/6	+	−	6/6	−	−
Dorsolateral premotor area (right hemisphere)	1/6	+	−	3/6	+	−
Dorsolateral premotor area (left hemisphere)	1/6	+	+	2/6	+	−
Supplementary motor area (right hemisphere)	0/6	+	−	1/6	−	−
Supplementary motor area (left hemisphere)	1/6	+	−	2/6	+	−

Number of healthy subjects (fMRI, left columns) with significant activations (active condition vs rest) of sensorimotor areas, cingulate motor areas, dorsolateral premotor areas and supplementary motor areas ($P < 0.0005$ for each voxel and $P < 0.05$ for spatial extent). Comparison with PET activations in patients I.M. ($P < 0.001$) and G.A. ($P < 0.01$) observed in the same cortical areas. Significant activation in the patients is indicated by + and lack of significant activation by −.

Patients

In patient I.M., strong contralateral activation of primary sensorimotor area could be seen during unimanual movements (Fig. 5). There was no activation of the left primary sensorimotor area during left-hand movements, even though we had observed small associated in-phase movements of the right hand (Fig. 2B, top right). During bimanual movements there was a clear additional signal in the cingulate cortex adjacent to the lesion and in the ventral SMA for both the in-phase and the anti-phase condition (Fig. 5). Interestingly, the significance of the cingulate activation was higher for in-phase than for anti-phase movements, which corresponded to a greater number of activated pixels, although movement rates were similar (Fig. 2B, bottom row; Table 2). A comparison with the activation pattern observed in normal subjects showed strong activation of the most dorsal part of SMA during bimanual movements in I.M., especially for her in-phase movements. Furthermore, there were additional activations of adjoining dorsolateral premotor and parietal areas.

In patient G.A. the level of activation was generally lower than in the first patient. However, as in patient I.M., contralateral sensorimotor areas became active during both right- and left-hand movements (Fig. 6), even though the activation was stronger for the left than for the right hemisphere. During bimanual movements significant activation of the primary sensorimotor area was seen only in the left hemisphere, with a reduction in the spatial extent during anti-phase compared with in-phase movements. The activation of the right primary sensorimotor areas was just below statistical significance. In contrast to patient I.M. and to normal subjects, there was no activation of the cingulate motor areas or SMA during any bimanual movements (Fig. 6; Table 3).

Neuropsychological testing

Imitation of pantomimed motor acts

Figure 7 shows the percentage of errors in imitating uni- and bimanual pantomimed motor acts. None of the two patients with cingulate lesions and none of the patients with SMA lesions reported elsewhere (Halsband *et al*., 1998) had difficulties in producing unimanual motor tasks from memory with their ipsi- or contralateral hand (Fig. 7, left). This was the case irrespective of whether the patients had to imitate symbolic gestures or meaningless movements in their personal or extrapersonal space.

In contrast to the intact performance during the unimanual condition, both patients with cingulate lesions had difficulties in the bimanual pantomimed motor task (Fig. 7, right). They showed severe impairment during the heterogeneous tasks when they were requested to use their two hands independently at the same time. When they were asked to perform identical movements simultaneously with both hands (homogeneous condition) patient G.A. exhibited a severe deficit, whereas patient I.M. showed a flawless performance. For comparison, patients with SMA lesions also exhibited their most pronounced difficulties in the heterogeneous condition. Normal controls had no difficulties in the imitation of pantomimed motor acts in any of the experimental conditions.

Sensory conditional learning: motor versus spatial selection

Figure 8 gives the mean number of errors for our two patients with cingulate lesions compared with controls (Halsband and Freund, 1990). Errors consisted of either an inappropriate choice of movement on the visual conditional motor task or the selection of a wrong spatial position, i.e. pointing to a circle which was not associated with the presented visual stimulus on the conditional spatial task.

The results indicate that patients were unimpaired when they had to recall a movement from memory on the basis of a visual cue (left side). This is in contrast to patients with SMA lesions, who made significantly more errors than controls (Mann–Whitney *U* test, $P < 0.01$) when they had to select between movements according to visual instructions (Halsband and Freund, 1990). Our patients showed no diffi-

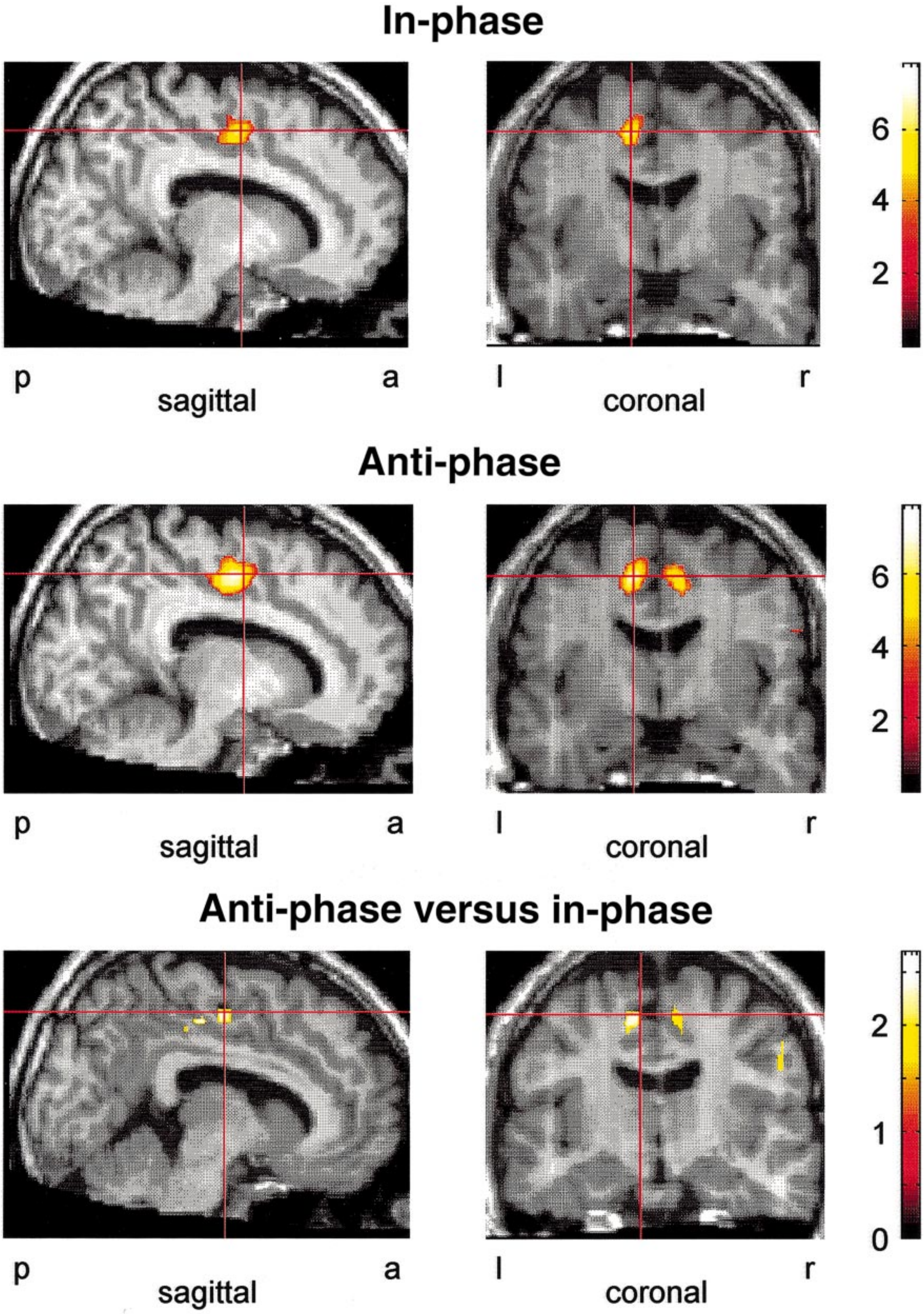


Fig. 4 Statistically significant signal increases obtained with fMRI in one of six healthy subjects performing bimanual in-phase and anti-phase tasks compared with rest and with each other. Bimanual in-phase movements compared with rest (threshold, $P < 0.001$; extent, $P < 0.05$) activated mesiofrontal structures just above the left cingulate sulcus (*upper panel*), while anti-phase movements compared with rest (threshold, $P < 0.001$; extent, $P < 0.05$) led to mesial frontal activity just above the cingulate sulci in both hemispheres (*middle panel*). Comparing directly the degree of activity between the anti-phase and in-phase conditions, statistically significant signal increases were found above the left and right cingulate sulcus at a lower level of significance ($P < 0.01$) (*lower panel*); on the left hemisphere its maximum appears slightly more dorsal than during in-phase movements.

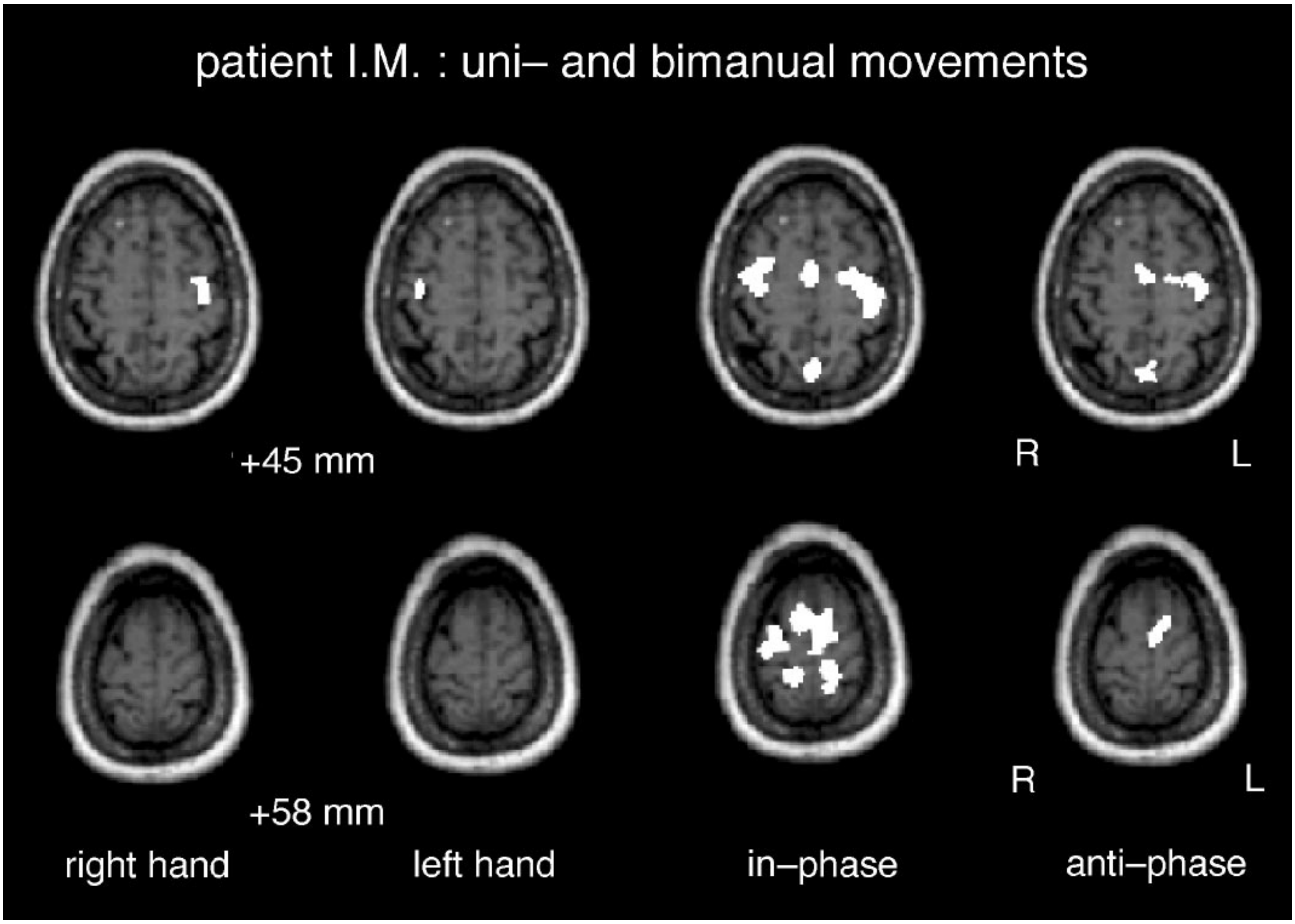


Fig. 5 Statistically significant increases in rCBF during uni- and bimanual movements of patient I.M. A clear contralateral activation of primary sensorimotor area can be seen during unimanual movements (*left panels*). During bimanual movements an additional signal was observed in the ventral medial wall dorsal to the lesion and supplementary motor area for the in-phase and the anti-phase conditions (*right panels*). There were also activations of adjacent dorsolateral premotor and parietal areas, especially during the in-phase condition.

culty in associating visual stimuli with spatial locations (right side).

Transcranial magnetic stimulation

Patient I.M. had normal central conduction times for both motor and sensory fibres. Routine motor evoked potentials showed central conduction times of 5.6 ms towards the right and 6.4 ms towards the left hand (first dorsal interosseus muscle) and of 14 ms towards the right and 14.2 ms towards the left leg (anterior tibial muscle). Latencies and amplitudes of somatosensory evoked potentials were also within the normal range. Transcallosally mediated inhibition was also normal (Fig. 9, black circles) when compared with a group of normal subjects (Fig. 9, black triangles): application of a conditioning stimulus to the right motor hand area 10–20 ms before the test stimulus delivered to the left motor cortex led to a marked reduction in the duration of the silent period in the right first dorsal interosseus muscle evoked by the test stimulus, indicating patent callosal conduction.

Patient G.A. also had normal motor evoked potentials: a central conduction time of 6.4 ms to both the first dorsal interosseus muscles and of 14.0 and 14.2 ms to the right and left anterior tibial muscles. Latencies and amplitudes of somatosensory evoked potentials were within the normal range. In contrast to patient I.M., there was no effective transcallosal inhibition: no reduction of the duration of the silent period was seen when the conditioning stimulus was given 10–20 ms before the test stimulus (Fig. 9, open circles).

Discussion

Our results provide evidence that bimanual co-ordination is orchestrated by multiple cortical regions including ventral and dorsal medial wall motor areas and dorsolateral premotor areas. Ventral medial wall lesions interfere with bimanual co-ordination in two aspects: impairment of bimanual synchrony (patient I.M. and patient G.A.) and pathological facilitation of associated movements (patient I.M.). In contrast to patients with SMA lesions (Halsband and Freund, 1990), our two

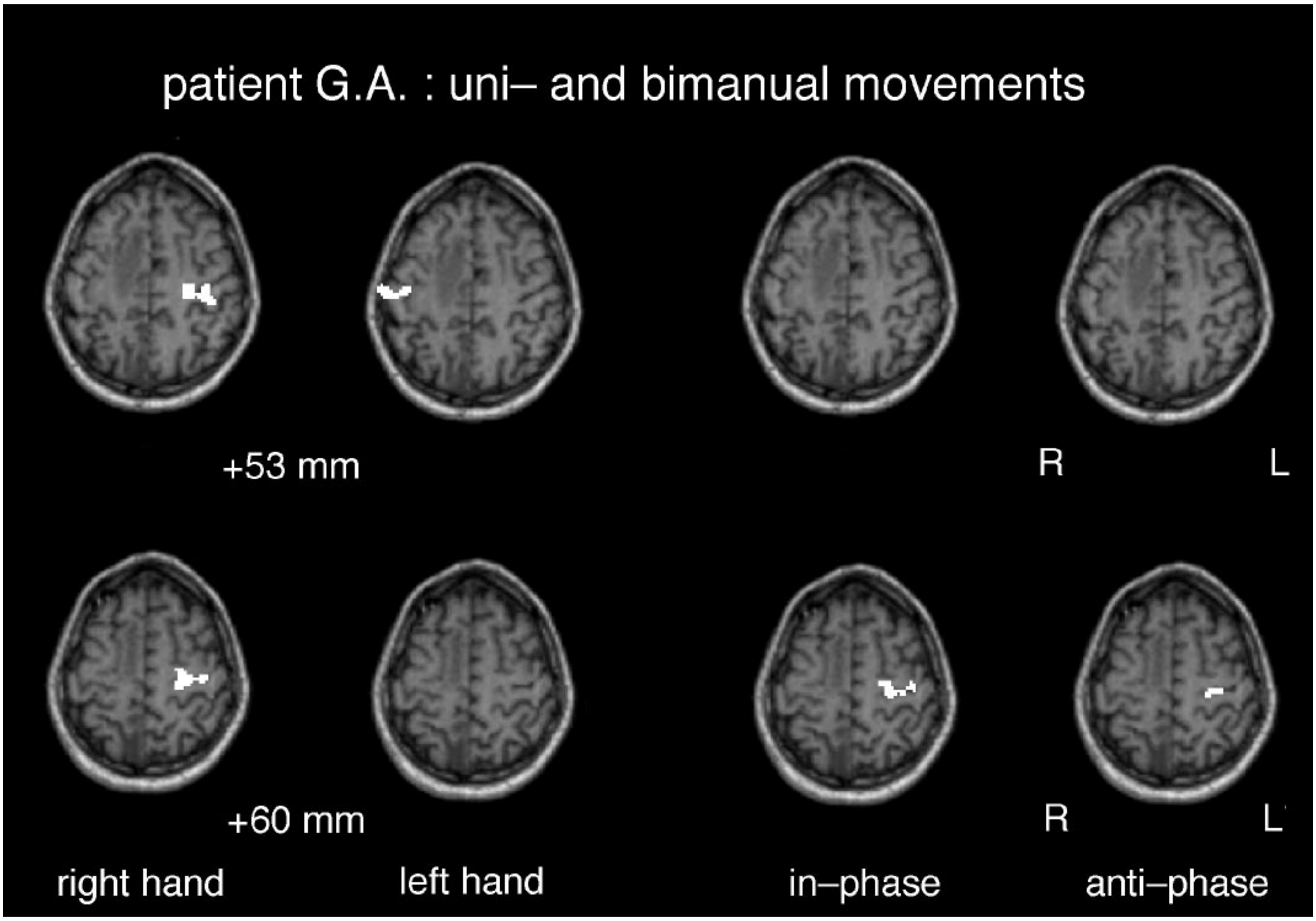


Fig. 6 Statistically significant increases in rCBF during uni- and bimanual movements of patient G.A. A clear contralateral activation of primary sensorimotor area can be seen during unimanual movements (*left panels*). However, activation was stronger for the left than for the right hemisphere. During bimanual movements, significant activation of the primary sensorimotor area at the $P = 0.01$ level was seen only in the left hemisphere. Activations in the right hemisphere had a lower statistical significance. In contrast to patient I.M., there was no statistical significant activation in the cingulate or supplementary motor area during bimanual movements (*right panels*).

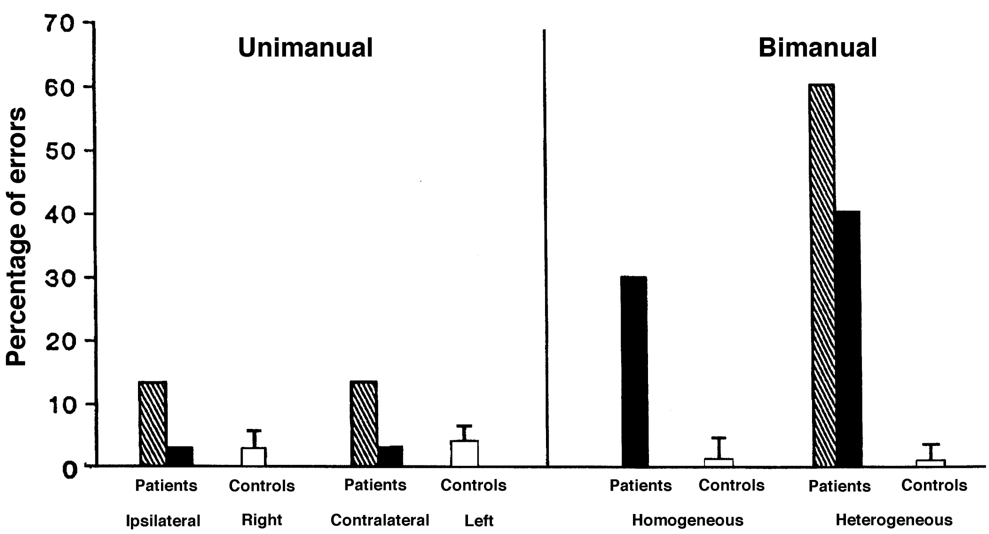


Fig. 7 Imitation of pantomimed uni- and bimanual motor acts in the two patients with cingulate lesions (I.M., cross-hatched columns; G.A., black columns) compared with normal controls (for details see text).

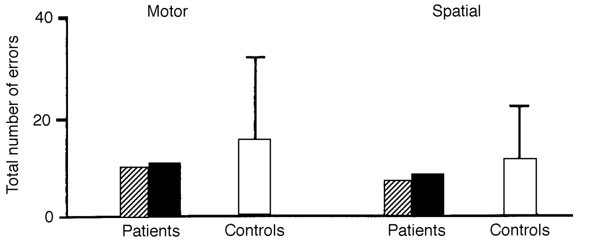


Fig. 8 Number of errors in sensory conditional learning tasks with motor and spatial selection. Results for the two patients with cingulate lesions (I.M., cross-hatched columns; G.A., black columns) compared with normal controls (for details see text).

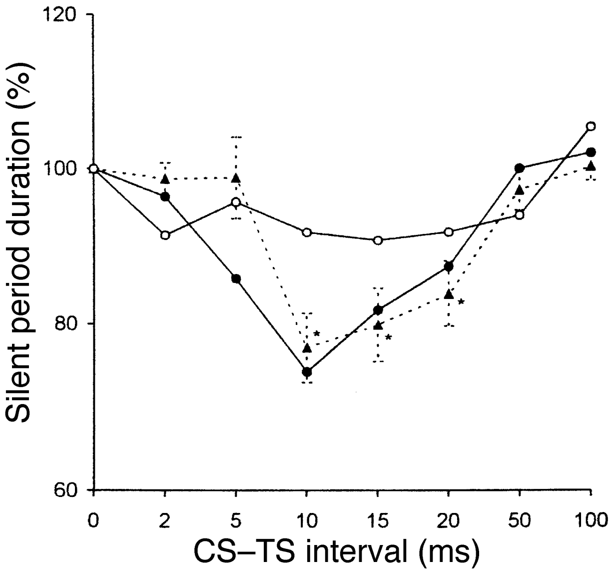


Fig. 9 Duration of the silent period in the right first dorsal interosseus muscle evoked by stimulation of the left motor cortex (test stimulus, TS) in relation to stimulation of the right motor cortex (conditioning stimulus, CS). The conditioning stimulus was given at different intervals prior to the test stimulus. Whereas the duration of the silent period was reduced in patient I.M. (filled circles) during the CS–TS interval of 10–20 ms, as in normal subjects (filled triangles) (Schnitzler *et al.*, 1996), no such reduction was observed in patient G.A. (open circles). $^*P < 0.05$.

patients had no problems with the early stages of motor planning, such as choosing the appropriate action in response to sensory cues. Further, in contrast to patients with callosotomy, who are preferentially impaired in the bilateral execution of complex temporal patterns, the combined callosal and ventral medial wall lesion in the second patient also interfered with the most basic temporal adjustment between the two hands: bilateral in-phase movements.

The bimanual task

In bimanual motor acts, it is usually the dominant hand that reaches out and manipulates the object while the other hand assists by stabilizing the object (Kazennikov *et al.*, 1994). There are only a few tasks in which the two hands move simultaneously. The present bimanual task demands such a synchronization of the two hands both in time and amplitude following well defined kinematic characteristics (e.g. Scholz and Kelso, 1989, 1990). Even though it is not a purposeful task and does not resemble a common daily activity, instructions are easy to follow and performance is easy to measure. Also, the in-phase and anti-phase movements involve the same muscle groups on the two sides and differ only with respect to their temporal patterns.

Outside the scanner, most of our normal subjects performed the anti-phase task slightly slower than the in-phase task (Table 2). The correlation between movements of the two hands was consistently higher for in-phase than for anti-phase movements. This is in line with several other studies that have demonstrated that in-phase movements represent a more stable movement pattern than out-of-phase and anti-phase movements (Scholz and Kelso, 1989, 1990). Furthermore, Byblow *et al.* (1994) observed involuntary phase-transitions from anti-phase to in-phase movements when movement rates were increased. During fast movements the motor system is obviously unable to sustain the anti-phase pattern and switches to the more stable in-phase pattern. Apart from the established bilateral limb asynergies in patients with premotor lesions (Freund and Hummelsheim, 1985), little is known about bimanual co-ordination deficits in neurological patients.

Lesion site and clinical deficits

At first sight, the clinical bimanual deficit of patient I.M., who had the pure right cingulate lesion, seemed to be more pronounced than that of patient G.A., who had the more extensive lesion of the right SMA, cingulate and corpus callosum.

Patient I.M. had problems performing simultaneous movements as soon as her hands were required to perform independently: e.g. tying shoe-laces, fastening buttons and during the experimental paradigm of bimanual anti-phase movements. She had no obvious problems with unimanual everyday movements or in performing identical movements simultaneously with both hands. Such a tendency towards simultaneous bilateral movements has also been associated with lesions of other parts of the medial wall; it has been observed in monkeys after ablation of the SMA and the upper bank of the cingulate sulcus (Brinkman, 1984) and in patients with mesiofrontal lesions involving either the SMA alone or the SMA and anterior cingulate (Laplane *et al.*, 1977; Chan and Ross, 1988). The lesion in patient I.M. was confined to the right ventral medial wall area below the cingulate sulcus. It will thus have affected either the cortical areas lining the lower aspect of the right cingulate sulcus and the middle aspect of the lower part of the interhemispheric sulcus or the fibres within the white matter connecting these areas with other ipsi- and contralateral structures.

Patient G.A. seemed to be relatively unaffected in daily life, although he had a much larger lesion, which also included the right SMA and corpus callosum. He had no problems tying shoe-laces and fastening buttons and at first sight he seemed to perform in-phase and anti-phase movements much better than patient I.M. Why then did he not show the same tendency towards simultaneous movements of his hands? Most likely this was due to the additional callosal lesion which interrupted at least some of the interhemispheric connections, as assessed by transcranial magnetic stimulation (Fig. 9). This may in turn have led to a greater degree of hemispheric and thereby manual independence, similar to the observations in the monkeys with ablation of the SMA and upper anterior cingulate, which also regained their manual independence after subsequent callosal section (Brinkman, 1984). Thus, the additional callosal lesion will have masked at least part of the bimanual deficit due to medial frontal lesions. Nevertheless the bimanual performance of patient G.A. was not perfect. He complained that he could not synchronize his hands while tapping a rhythm and he was not able to pantomime any two-handed action on command.

Underlying common principles for bimanual co-ordination

Even though the clinical deficits of the two patients were quite different, kinematic analysis of their movement patterns revealed that these deficits can be explained by an underlying common pattern of motor disturbances.

Both patients showed not only deficits in bimanual co-ordination, although these were most prominent, but also slight abnormalities during unimanual movements. Both patients showed substandard performance of the left hand during simple movements in the motor function test battery (Table 1). In patient I.M. the kinematic analysis during unimanual left hand movements showed symmetrical co-activation of the right hand (Fig. 2B, top right). She was not able to suppress these movements even with visual feedback. No such ‘mirror movements’ ipsilateral to the lesion were observed in patient G.A. These results suggest that the observed deficit is not specific for bimanual movements, but its effect is most prominent during these movements. In patient I.M. the loss of suppression of coupled simultaneous movements of the ipsilesional hand can explain her failure to establish the anti-phase coupling mode successfully (Fig. 2B, bottom right; Fig. 3C). This deficit was restricted to a deficit of simultaneous independent movements of the two hands. Sequential bimanual movements were not impaired. This also applied to pantomime movements: while she could not pour pudding powder into milk with her left hand while simultaneously stirring it with her right hand, she had no problem performing this task sequentially. In patient G.A., movements were never exactly simultaneous even during the in-phase condition (Fig. 3E). Strictly speaking, all his movements were therefore performed sequentially, although the time lag between the two sides was so small that they appeared to be simultaneous in everyday life.

However, the two hands were not completely uncoupled in patient G.A. Kinematic analysis showed a change in coupling mode during both bimanual in-phase and anti-phase movements (Fig. 3E and F) with a tendency towards an oscillatory pattern. In patients with lesions or agenesis of the corpus callosum, such difficulties of bimanual co-ordination are common (e.g. Geffen *et al*., 1994), especially when they are required to perform asynchronously co-ordinated bilateral movements (Zaidel and Sperry, 1977). These difficulties persist even when the rhythm of both types of movement is externally paced (Tuller and Kelso, 1989). In contrast to patient G.A., however, these patients with callosal agenesis or callosal lesions have no problems performing movements synchronously with both hands during simple in-phase tasks (Zaidel and Sperry, 1977), although the amplitude may show greater variation than in normal subjects (Tuller and Kelso, 1989). This breakdown of bimanual synchrony during the in-phase condition in patient G.A. is probably the consequence of the additional cingulate lesion. Such a lack of synchrony also became apparent in patient I.M. with regard to amplitude in the bimanual in-phase condition (Fig. 2B, bottom left). This lack of bilateral synchrony was especially pronounced while she was lying on the PET scanner and deprived of visual feedback. It was still present when we investigated this patient a second time about 18 months later.

In summary, the kinematic patterns of both patients provide evidence that ventral medial wall areas play a pivotal role in the establishment of (i) unimanual independence and (ii) accurate temporal adjustments between the two hands. Furthermore, while damage of the corpus callosum may mask some sequelae of ventral medial wall function (loss of contralateral suppression), it cannot restore other aspects of the movements, such as bilateral synchronization.

Functional imaging in healthy subjects

The importance of ventral medial wall areas for these temporal aspects of bimanual co-ordination are supported by the functional imaging results obtained in our volunteers. They showed activations just above the left cingulate sulcus during the in-phase condition and an increase in activity in both right and left areas above the cingulate sulci during the anti-phase condition (Fig. 4; Table 3). Both in-phase and anti-phase movements require synchronization between the two hands, but only anti-phase movements also depend on effective contralateral suppression. This increase in the complexity of temporal motor control was associated with an increase in activity within the right and left ventral medial wall areas in all six subjects (e.g. Fig. 4).

Within the medial wall, activity was mainly observed at or close to the opening of the cingulate sulcus. Such activations within cingulate sulcal areas are generally described as cingulate activations (Picard and Strick, 1996), although cytoarchitectonic data do not yet exist to describe where the border between the cingulate area and the supplementary motor area is located in man. Therefore, ventral SMA may also be involved. During bimanual movements, the exact location of the foci of midline activations varied considerably between subjects within these ventral medial wall areas either within or just above the cingulate sulci. Moreover, even within subjects several foci can be demonstrated in these ventral midline areas at lower levels of statistical significance, especially during the anti-phase condition, indicating that there is not just one ventral medial wall area on either hemisphere but an array of different areas within the depths and at the opening of the cingulate sulci. The observation of such an array of cingulate motor areas is in line with recent observations in monkeys, where at least three different cingulate motor areas have been identified (He *et al*., 1995). In patient I.M., the lesion was below the cingulate sulcus and thus it may have affected the connections towards only some of these cortical areas situated in the lower bank of the cingulate sulci. The pathophysiological disturbances observed in the patients are thus not typical of the dysfunction of a single area within the ventral medial wall, but are more likely to be due to disturbed interactions of several ventral medial wall areas with each other and with other ipsi- and contralateral areas.

Specificity of ventral medial wall motor areas

We have shown that two special aspects of bimanual co-ordination may be related to the function of the ventral medial wall areas. But in which way are these functions specific to these areas, especially when compared with the dorsal medial wall and ventral premotor areas?

The array of ventral medial wall areas can be contrasted with the dorsal medial wall areas encompassing the SMA. Generally, the SMA is suggested to be involved in higher aspects of sensorimotor functions, including ideation and the planning and initiation of motor tasks; the cingulate motor areas are more closely related to the actual execution of motor commands (e.g. Dettmers *et al*., 1995). Our results support this concept of different functions for the two medial wall areas. In healthy subjects we observed the main focus of activity within the ventral but not in the dorsal medial wall areas. In contrast, much stronger SMA activations have been observed during slightly more complex tasks, such as uni- and bimanual movements in space (e.g. Stephan *et al*., 1995; Stephan *et al*., 1998). Neuropsychological testing showed that, in contrast to patients with SMA lesions (Halsband *et al.*, 1998), our two patients were not impaired in visuomotor association learning (Fig. 8), even though patient G.A. had some oedema of his right SMA (Fig. 1). Furthermore, we know that not only the execution but also the mental concept formation of associated motor responses is often impaired in patients with lesions of the SMA and lateral premotor areas. This capacity was, however, not impaired in our two patients. Both knew what to do and had a concept of how to perform these bimanual movements.

Thus, with regard to bimanual co-ordination, the dorsal SMA may be one of the areas which contributes to general integrative aspects of interhemispheric interactions. This assumption is supported by results of Viallet *et al*. (1992), who observed inhibitory functions exhibited by neuronal populations within SMA not during the execution but during the planning stages of bimanual movements. Similarly, when Kermadi *et al.* (1997) reversibly inactivated the SMA in two monkeys, they found that the initiation of a co-ordinated movement of the two forelimbs and the two hands was disturbed, but not the actual execution of the bimanual drawer-pulling and grasping sequence. In contrast, we suggest that the ventral medial wall motor areas may be preferentially involved in more basic facilitatory and inhibitory processes, e.g. with regard to the present experimental paradigm: (i) to co-ordinate bimanual movements by means of stabilizing in-phase and anti-phase patterns between the two sides and (ii) to ensure successful 'uncoupling' of the two hands during movements of only one hand.

This distinction of bimanual function is even more difficult for lateral premotor areas compared with medial wall areas, as there are few studies which have investigated the nature of bimanual motor deficit in patients with premotor lesions in kinematic detail. Furthermore, there are very few patients with focal lesions in whom it is possible to attribute an observed deficit to a well localized anatomical area. Freund and Hummelsheim (1985) found that patients with premotor lesions showed a disturbance of unilateral proximal movements but in particular of co-ordination between the two sides. Deficits in uni- and bimanual rhythm production in these patients (Halsband *et al*., 1993) support the view of a deficit in temporal aspects of motor programming. Such a disintegration of the dynamics of the motor act has already been observed by Luria (1966) for unimanual movements as a sequel to premotor lesions.

In the monkey, the dorsolateral premotor areas have strong connections to parietal areas and appear to be involved in the planning and controlling of arm and leg movements on the basis of somatosensory and visual information (for review, see Rizzolatti *et al*., 1998). Thus, one would expect that the integration of sensory information into the bimanual movement plan should be another hallmark of dorsolateral premotor function. Halsband and Freund (1990) have indeed observed deficits of unimanual conditional movement selection in patients with premotor lesions. The difference between patients with medial and lateral lesions was, however, not as clear-cut as would have been predicted by theoretical models based on the monkey data.

Compensatory strategies

Functional imaging studies in patients are often seen as one way to identify the compensatory strategies used by patients in order to achieve their goals. Are we then to conclude that only patient I.M. activated additional premotor and parietal circuits (Fig. 5) when she tried to compensate for her clinical deficit, while patient G.A., who showed hardly any premotor, parietal or midline activity, did not attempt to compensate for his deficits? The altered activation pattern in these two patients provides a good indication that such reasoning is too simple. The observed rCBF changes may also be due to (i) a direct effect of the tumour and (ii) the altered performance of the task itself, as well as (iii) the compensatory strategies.

(i) While isomorphic brain tumours, such as the low-grade astrocytoma in patient I.M., may lead to alterations of motor representations, anaplastic tumours and their oedema, as in patient G.A., can alter the haemodynamic regulation and thereby result in shifts of activation peaks and a reduction in the significance of rCBF changes (Wunderlich *et al.*, 1998). Thus, the lack of significant activation of the cingulate, SMA and primary sensorimotor cortices of the affected right hemispheres in patient G.A. can be explained by a direct effect of the tumour and cannot be taken as proof that the right hemisphere is not involved in bimanual processing. Furthermore, remote effects of the tumour may account for the lack of medial activation also in the unaffected left hemisphere.

(ii) Motor performance of the two patients differed from that of the healthy volunteers: kinematic recordings of the bimanual movements of both patients, especially of patient I.M., showed irregular frequencies and amplitudes. This change was, however, not accompanied by a significant change in maximal frequency during the anti-phase compared with the in-phase movements (Table 2), which could explain a reduction in activity in the medial premotor or primary sensorimotor areas in either of the two patients during these anti-phase movements (Figs 5 and 6; Schlaug *et al.*, 1994).

(iii) Both patients were aware that they performed their bimanual tasks slightly differently compared with normal subjects. Patient I.M. actively tried to overcome her difficulties. She reported that during the in-phase movements she noticed the irregular amplitudes. Presumably, the prominent activation of the 'full network' of cortical motor areas, including the dorsal SMA, dorsal premotor areas and additional parietal areas (Fig. 5), reflected increased focusing on sensory feedback as well as the permanent effort of motor planning and motor execution. In contrast, the activation pattern during the anti-phase movements might reflect her principal effort to suppress time-locked in-phase movements. Patient G.A. knew that he was not able to perform the in-phase and anti-phase movements synchronously. He told us he would perform as well as he could but would not engage in the 'fruitless' effort of trying hard to achieve something he knew he could not do. During both the in-phase and the anti-phase condition, he therefore did not continuously monitor and plan his movements, as did patient I.M. This may be another reason why no medial wall activations and especially no SMA activations were observed in either of his two bimanual conditions.

Comparative lesion-activation studies

Our study provides an interesting perspective on the comparative lesion-activation studies approach. Such a combined approach represents a powerful tool for investigating brain function both in the human and in experimental animal studies. The combination of neuronal activation with the functional deficits and the deactivation provides complementary information about the function of the circuitry under investigation. Whereas the activation studies show the network involved in bimanual activities, the significance of particular nodal points becomes clear from the information gained in the lesion study. Our combined study is a good example of how the 'weighting' factor of certain network components is disclosed by the lesion-based information. The better integration of activations around areas with focal brain damage remains an issue for future research.

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