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Functional reorganization of brain in children affected with congenital hemiplegia: fMRI study

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Abstract

Using functional magnetic resonance imaging, the brain activation related to unilateral sequential finger-to-thumb opposition was studied in six children with a right congenital hemiplegia of cortical origin. They were compared to six age-matched controls. In the control group, movements with either hand asymmetrically activated the sensorimotor cortex and premotor areas in both cerebral hemispheres with a typical contralateral predominance. By contrast, paretic finger movements activated both hemispheres in the hemiplegic patients, with a strong ipsilateral predominance favoring the undamaged hemisphere. The activation induced by nonparetic finger movements was restricted to the contralateral undamaged hemisphere. Furthermore, the level of activation in the undamaged cortex was partly related to residual finger dexterity, according to covariance analysis. These activation patterns indicate an adaptive reorganization of the cortical motor networks in this group of patients, with a prominent involvement of the undamaged hemisphere in the control of finger movements with either hand.

Keywords: Cerebral palsy; Plasticity; Digital skills; Motor cortex; fMRI; Activation

Introduction

In primates including humans, one of the most harmful consequences of an acquired injury of the corticospinal tract is the impairment of highly skilled hand abilities requiring the performance of relatively independent finger movements (Forssberg et al., 1999). Moreover, the development of fine manipulative skills is irremediably impaired in monkeys subjected to such an injury during the perinatal period (Lawrence and Hopkins, 1976; Passingham et al., 1983; Rouiller et al., 1998). This has been observed despite a dramatic functional recovery of the other motor behaviors, such as climbing or jumping. Similarly, in man, a unilateral intrauterine or perinatal brain injury of the motor cortical areas or their corticospinal projections results in congenital hemiplegia which is characterized by spasticity and by various motor disabilities (Aicardi and Bax, 1998). Children affected by hemiplegic cerebral palsy can exhibit prominent impairment in the realization of skilled voluntary movements. In particular, the precision grip between the thumb and index pads requiring the performance of precise independent finger movements can be notably impaired (Forssberg et al., 1999; Eliasson and Gordon, 2000).

A profound functional and structural reorganization of the central nervous system—commonly referred to as cerebral plasticity — can occur in the adult central ner-

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vous system in response to a brain injury. Positron emission tomography and functional magnetic resonance imaging (fMRI) studies in adult hemiparetic patients who recovered from a unilateral stroke indicated that the undamaged hemisphere may be involved in the functional recovery of the ipsilateral paretic hand (Chollet et al., 1991; Cramer et al., 1997). Using combined fMRI and task disruption by transcranial magnetic stimulation (TMS) during finger movements in adult stroke patients, Johansen-Berg et al. (2002a) showed that the dorsal premotor cortex of the undamaged hemisphere was directly involved in functional recovery of the ipsilateral paretic hand, particularly in the more impaired patients. Such an interhemispheric functional reorganization might be even more pronounced after early brain injury, leading to the suggestion that the undamaged hemisphere could take over the control of the ipsilateral paretic hand in patients with congenital hemiplegia (Carr et al., 1993; Cao et al., 1994; Müller et al., 1998a, 1998b; Nirkko et al., 1997; Macdonell et al., 1999; Thickbroom et al., 2001; Staudt et al., 2002). This is in accordance with the generally admitted hypothesis that the immature brain has a greater potential for functional reorganization thanks to the dramatic ease of the immature neurons in modifying their connections (Payne and Lomber, 2001, and references therein). However, the functional relevance of the activation of the undamaged hemisphere during paretic hand movements could be obscured by the frequent occurrence of mirror movements (MM) in the passive nonparetic hand and/or by a possible imbalance between the transcallosal inhibitory connections (Boroojerdi et al., 1996; Staudt et al., 2002; Vandermeeren et al., 2002a). The origin of MM, which can be seen in young children (Woods and Teuber, 1978) and in patients with congenital hemiplegia (Carr et al., 1993), unilateral brain malformation (Holloway et al. 2000) or Kallmann's syndrome (Krams et al., 1997; Mayston et al., 1997) is uncertain. Since most studies excluded a significant reorganization of the spinal cord circuitry to account for MM in the nonparetic hand, two main hypotheses have been formulated to explain the MM in patients with congenital hemiplegia. First, a strengthening of the ipsilateral connections that are present from childhood could have been promoted by the functional demand, due to the contralateral brain damage. Accordingly, the undamaged hemisphere would have taken over the control of the paretic hand through ipsilateral corticospinal projections, whereas the concomitant recruitment of crossed projections from the same hemisphere would induce MM in the contralateral, nonparetic hand. Such a hypothesis would predict a preferential activation of the undamaged primary motor cortex during voluntary movements of the paretic hand. Second, MM may result from a reduction of transcallosal inhibitory activity from the damaged hemisphere during cortical maturation through childhood, resulting in simultaneous activation of both motor cortices during intended unilateral movement. Such a hypothesis would predict a bilateral activation of brain motor areas, with a significant contribution of the damaged hemisphere in the control of paretic hand movement, provided the lesion is not too diffuse (Holloway et al., 2000). To what extent the undamaged and damaged hemispheres of congenital hemiplegics are respectively involved in the fine control of independent finger movements of the paretic hand or in the generation of MM is thus still a matter of debate. In addition, since both hemispheres are involved in the performance of skilled finger movements with either hand in normal subjects (Kim et al., 1993; Chen et al., 1997; Nirkko et al., 2001), it is likely that an early brain injury may induce a reorganization of the cortical network involved in the control of the nonparetic finger movements as well. This issue has not received much attention in previous functional brain imaging studies about stroke or congenital hemiplegia. Most often, the activation pattern related to nonparetic hand movements has been reported to be roughly comparable to that observed in control subjects (Chollet et al., 1991; Sabatini et al., 1994; Cramer et al., 1997; Cao et al., 1998; Müller et al., 1998b), although its has repeatedly been demonstrated that a unilateral brain damage also impairs the function of the nonparetic upper limb in either congenital hemiplegics or adult stroke patients (Jones et al., 1989; Gordon et al., 1999).

To gain further insight into these questions, we investigated the fMRI activation patterns elicited by paretic and by nonparetic finger movements in a group of children with congenital hemiplegia who were affected by unilateral cortical lesions. The activation patterns were compared with those obtained during finger movements in a group of age-matched control children, with a special emphasis on the relationships with mirror movements and digital dexterity. In particular, in an attempt to uncover the actual involvement of the damaged and undamaged hemispheres in the control of paretic finger movements in hemiplegic patients, covariate analyses between the fMRI activation and the residual digital dexterity or the intensity of mirror movements were computed.

Materials and methods

Subjects

Six children with congenital hemiplegia (12.3 ± 3.4 years, mean ± SD) and six sex- and age-matched control subjects (12.7 ± 3.2 years, $t = -0.17$, $P = 0.86$) were included in this study. A right hemiplegia detected during the first postnatal year and resulting from a left cortical injury was the inclusion criterion for the patients. All the procedures were approved by the Ethical Committee of the Université Catholique de Louvain. Both parents of each subject gave written informed consent before the study.

Table 1
Patients with congenital hemiplegia: clinical and MRI descriptions

Patient	Sex	Age (years)	History	Clinical description	Clinical scores	Cerebral lesions (MRI)
1	M	9	BW 4.500, walk 15, SL borderline	R hemiparesis, R hand disuse, epilepsy, spasticity (3-3), MM (0-2-1/2-2-3)	FIM 123, Brunn 36, Melb 55, PPT 0.3/11.3	Deep L MCA lesion with MCE of the lenticular and caudate nuclei, internal and external capsula, with L VM and L thalamus hypotrophy
2	M	10	BW 3.460, walk 16, SL normal	R hemiparesis with equinus, R hand disuse, spasticity (1-2), MM (3-2-2/4-3-4)	FIM 124, Brunn 65, Melb 70.5, PPT 1.3/14.7	Closed-lip schizencephaly in the L central sulcus, lined by polymicrogyria, mild L VM and L thalamus hypotrophy
3	M	10	BW 3.500, walk 15, SL normal	R hemiparesis, R hand disuse, epilepsy, spasticity (1-2), MM (3-3-3/3-2-3)	FIM 124, Brunn 21, Melb NA, PPT 0/12	Large L MCA lesion with MCE in the frontoparietal cortex and insula, mild L VM, L hemisphere and thalamus hypotrophy
4	F	12	PB 29 weeks, BW 1.500, walk 17, SL normal	R hemiparesis, R hand disuse, epilepsy, spasticity (2-3), MM (0-0-1/2-3-1), astereognosis	FIM NA, Brunn 44, Melb NA, PPT 1/11	L MCA lesion with MCE in the frontoparietal cortex, mild L VM, mild L hemisphere hypotrophy
5	F	16	BW 3.170, walk 14, SL normal	R hemiparesis with equinus, R hand disuse, spasticity (1-3), MM (1-1-1/1-3-2)	FIM 126, Brunn 69, Melb 86, PPT 2.3/15.3	L MCA lesion with MCE in the frontoparietal cortex, mild L VM, L hemisphere and thalamus hypotrophy
6	F	17	PB 30 weeks, BW 1.400, walk 24, SL normal	R hemiparesis with equinus, spasticity (1-2), MM (0-0-0/0-1-1)	FIM 126, Brunn 89, Melb 100, PPT 11/17.3	L MCA lesion with MCE in the temporoparietal cortex, mild L VM

PB, premature birth; BW, birth weight (kg); walk, age at walking acquisition (months); SL, school level at the time of fMRI; R, right; L, left; scoring for spasticity (upper–lower limb) was on a 0 to 4 basis (Ashworth scale) and refers to the limb part mostly affected; MM, mirror movements score (0–4) observed in paretic/nonparetic hand during movement (finger tapping, fist rotation, sequential opposition) of the opposite hand; FIM, functional independence measure (normal value, 126); Brunn, Brunnstrom score (normal value, 90); Melb, Melbourne score (normal value, 100); PPT, score for digital dexterity in the Purdue Pegboard Test is the mean number of small pegs inserted in board holes in 30 s using the paretic/nonparetic hand (normal values obtained in control children were 16.4 ± 1.2 and 15.1 ± 1.2, respectively, for the right and left hands); NA, not available; MCA, middle cerebral artery territory; MCE, macrocystic encephalomalacia; VM, ventriculomegaly (see text for additional details).

The history and clinical descriptions of hemiplegic children are listed in Table 1. Briefly, the perinatal history was negative except for premature birth in cases 4 and 6. Early mental and speech development was normal (i.e., with sentences before 2.5 years). At the time of this study, mild to moderate motor weakness (Claeys et al., 1983) and dyspraxia of the right hand were observed in all cases, as well as mirror movements in the left hand (Table 1). Pyramidal symptoms such as hyperreflexia, involving upper and lower limbs, and a Babinski sign were present in all patients. In addition, patients 1, 3, and 4 were affected by a well-controlled partial complex epilepsy. There were no left-handed subjects among parents or relatives.

Anatomical MRI showed a left cortical or cortico-subcortical lesion with mild left ventriculomegaly in all patients. Patient 2 had a left frontal, closed-lip schizencephalic cleft lined by abnormally thickened cortex with white matter trabecula, suggesting a polymicrogyria. The other patients exhibited cystic lesions compatible with perinatal infarctions (Table 1).

The controls were normal on neurological examination; they were all right-handed (Olfield, 1971), had a normal MRI, and had a normal school level at the time of study.

Clinical evaluations

In each subject, the limb spasticity was evaluated using the Ashworth scale (Ashworth, 1964) (see Table 1). The degree of sensorimotor impairment in the upper limb was evaluated by means of the Brunnstrom Scale (Brunnstrom, 1966) and the Melbourne Assessment, a test recently designed for children with neurological impairment, which scores reaching, grasping, releasing, or manipulating objects (Randall et al., 2001). The impairment of highly skilled finger movements of each hand was evaluated by the Purdue Pegboard Test (PPT), which scores the maximal number of small pegs inserted into the holes of a board in 30 s using one single hand (Mathiowetz et al., 1986). The PPT is currently considered one of the most reliable estimates of the digital dexterity both in normal subjects and patients (Backman et al., 1992) and in school-age children (Smith et al., 2000). In the present study, each subject (control or patient) was tested with the PPT and the mean result of three

trials with either hand was used as individual score for digital dexterity of the related hand. MM in the passive upper limb were scored from 0 (absent) to 4 (identical to the voluntary movements of the intended hand) during finger tapping, fist rotation, and sequential fingers-to-thumb opposition (Woods and Teuber, 1978). In addition, the level of global disability was assessed by means of the Functional Independence Measure (FIM) (Keith et al., 1987), which scores the degree of assistance in daily life activities such as locomotion, dressing, and feeding. The results of the sensorimotor impairment scores we observed in our patients are presented in Table 1.

fMRI task and EMG recording

Before the fMRI session, the subjects were allowed to practice the activation task, a self-paced repetitive fingers-to-thumb opposition with the elbow flexed at about 90°, in the supine position with eyes closed. The rate of movement was not recorded inside the magnet. Despite the spasticity and motor impairment, all patients were able to achieve the task with the fingers of the paretic hand, although with slowness and progressive tiredness.

Surface electromyography results (EMG) of both the flexor digitorum superficialis (FDS) and abductor pollicis brevis (APB) or first dorsal interosseous (FDI) were bilaterally recorded outside the magnet during sequential finger opposition. EMG was amplified (gain, 500–2000, cutoff frequency, 5–2.500 Hz, Neurolog, Digitimer, UK) and digitized at 5 kHz using a personal computer with a 1401 interface (Cambridge Electronic Design, UK) for offline analysis.

3D MRI and fMRI acquisition

Structural brain imaging was obtained in all subjects by 3D MRI in the axial plane orientation on a 1.5-T unit (GE Signa, Milwaukee, WI, USA) using a T1-weighted gradient echo sequence (SPoiled GRass, TR, 25 ms; TE, 6 ms; flip angle, 25°; slice thickness, 1.5 mm). The head was restrained by chin and front straps and by foam pads.

Blood oxygen level-dependent (BOLD) fMRI data were acquired using a multislice gradient echo–echo planar imaging (GE-EPI) sequence (TR, 4500 ms; TE, 50 ms) with 31 axial slices, 3.8 mm slice thickness (isotropic voxel), in the AC–PC orientation (i.e., in the plane of the anterior and posterior commissures, Talairach and Tournoux, 1988). The matrix was 64×64 and the field of view was 240 mm.

The fMRI paradigm consisted of 14 alternating epochs of self-paced repetitive sequential fingers-to-thumb opposition and rest (27 s per epoch, six repetitions, except for the first epoch, which lasted 36 s, with eight repetitions). Each hand was assessed in a separate run while the eyes remained closed, always beginning with the nonparetic (dominant) hand. The cue to start and to stop unilateral finger movements was a gentle touch on the leg ipsilateral to the target hand. Investigators visually checked the task performance and the presence of mirror movements in the passive hand that was manually restrained in patients by one investigator, throughout the run, in attempt to minimize the motion artifacts.

fMRI processing

The first 4.5 s of each fMRI acquisition was discarded due to unsteady magnetization. The individual 3D SPGR volume was realigned to the first remaining fMRI scan of the corresponding subject using an interactive homemade image display software (Michel et al., 1995) implemented in IDL language (IDL Research Systems, Inc.), using the dual exchanged isocontours procedures (Pietrzyk et al., 1994). Using SPM99 (The Wellcome Department of Cognitive Neurology, London, UK, implemented in Matlab; Mathworks Inc.), the 3D SPGR volume was then spatially normalized into the referential defined by the atlas of Talairach and Tournoux (1988) and the MRI template supplied by the Montreal Neurological Institute (MNI), following a protocol described previously (Vandermeeren et al., 2002b). Special care was taken to avoid "overnormalization" of the MRI by masking the area of the lesion and of the deformed structures, excluding these brain regions from the normalization process (Brett et al., 2001). The fMRI data were then spatially realigned using a least squares approach to estimate a six-parameter rigid body transformation for each scan (SINC interpolation) (Friston et al., 1995a) and further spatially normalized in one single step using the normalization parameters derived from the 3D SPGR normalization. This procedure resulted in normalized fMRI scans with a cubic voxel size (2×2×2 mm) for group analysis. These images were further spatially smoothed with an isotropic Gaussian kernel (4 mm full width at half maximum, FWHM) in order to reduce the residual anatomical and functional variability between subjects.

Statistical analysis

The condition effect [activation–rest] was separately estimated for each hand of each subject using the general linear model (Friston et al., 1995b). In a single subject analysis, statistics were computed with SPM99 for each voxel using a delayed boxcar function as the reference waveform for modeling the haemodynamic responses. Statistical parametric maps (SPM) of the t values (SPM $\{t\}$) were transformed in the unit normal distribution (SPM $\{Z\}$). Voxels with a level of statistical significance of $P < 0.05$ (corrected for multiple comparisons) were considered significantly activated and only voxels clusters with an extent (k) superior to 20 voxels were considered.

A fixed effect (FFX) analysis was carried out to show the activation patterns related to voluntary movements of the fingers in the two groups. First, the condition effect [activation–rest] of the right (paretic in patients) and left (non-

paretic) fingers were computed separately in each group. Second, these patterns were compared between the controls and patient groups for each hand. The related condition effect [activation–rest] was used as inclusive mask for each of these last comparisons (i.e., the contrast [Patients–Controls] was masked by [activation–rest] in the patients group to ensure that all activated voxels in [Patients–Controls] were due to real activation above the basal resting state in Patients and not to deactivation in Controls).

A random effect (RFX) analysis was also carried out since this second level analysis is generally considered the gold standard for fMRI group analysis and allows us to make inferences at the population level (Holmes and Friston, 1998). The SPM "contrast" images, which summarized the fMRI activation related to each hand of each individual subject in FFX analysis, were fed in the appropriate statistical models provided by SPM99 for RFX analyses. First, differential activation between the patients and control subjects was computed (two-sample *t* test), respectively, for the right and left hands, in order to confirm the differential activation between groups that was disclosed by the first level (FFX) analysis. Second, a RFX covariate analysis was carried out (linear regression) to examine whether a substantial part of the fMRI activation could be explained by the influence of (1) age, (2) mirror movement in the passive hand (using the sequential fingers opposition MM subscore of the passive hand as a covariate), or (3) digital dexterity of the active hand (using the Purdue Pegboard Test score, which shares with sequential finger opposition (fMRI task) the performance of relatively independent finger movements).

Results

Clinical results

The patients with congenital hemiplegia showed a variable functional impairment of the right upper limb (Brunnstrom score, 54 ± 24.8; mean ± SD, $n = 6$, normal value, 90), this impairment ranged from severe (55/100) to absent (100/100) as reflected by the Melbourne score (Table 1). However, the patients were relatively independent (FIM range, 123–126/126). All patients also had poor scores at the Purdue Pegboard Test with the right paretic hand (number of pegs inserted in board holes in 30 s, 2.6 ± 4.2, mean ± SD), whereas the score of the left nonparetic hand was 13.6 ± 2.5; this reflected a severe impairment of digital dexterity in the paretic hand ($t = -10.3$, $P < 0.001$, paired *t* test). By contrast, the control subjects realized a mean PPT score of 16.4 ± 1.2 with the right hand and of 15.1 ± 1.2 with the left hand ($t = 2.5$, $P = 0.06$). The group difference was significant for the right hand ($t = -9.2$, $P < 0.001$) but not for the left hand ($t = -1.79$, $P = 0.133$), although the scores obtained by all patients but one (No. 6) with their left nonparetic hand were lower than those observed in controls with their right dominant hand ($t = 3.8$, $P = 0.01$). Patient 6 differed from the other cases by the absence of functional impairment on the Melbourne test. In the patient group, this patient also had the highest scores on the PPT but still scored at < 3 SD from controls for the right paretic hand (Table 1).

Most of the patients exhibited strong MM in the passive nonparetic and paretic upper limbs, including during the fMRI task performance (see Table 1). A clear mirroring EMG activity during sequential finger opposition was observed in patients 2 and 3. In the two youngest controls, scarce and intermittent MM were observed in the right (grade 1) and left (grade 1 to 2) upper limb but no consistent mirroring EMG activity was recorded in these subjects.

fMRI pattern during right dominant hand movements in controls

In the control group, right sequential finger opposition activated a bilaterally distributed network of cortical areas with a leftward predominance (FFX analysis, Fig. 1). This network included bilaterally the primary sensorimotor cortices (S1M1, Brodmann areas (BA) 1, 2, 3, and 4) and the premotor cortices (PM, lateral BA 6) (Table 2). The right and left supplementary motor areas (SMA, mesial BA 6), the left thalamus, the right superior parietal lobule (SPL, BA 7), and the left inferior parietal lobule (IPL, BA 40) were also activated. Both cerebellar hemispheres were also activated (right more than left).

The RFX covariate analysis did not reveal any correlation between the cerebral activation evoked by right sequential finger opposition and age, MM score in the left hand, or Purdue Pegboard Test score of the right hand (threshold for analysis, $P = 0.001$, uncorrected).

fMRI pattern during right paretic hand movements in hemiplegic patients

In the patient group, the activation pattern elicited by paretic finger movements engaged both hemispheres as in controls. However, this activation was more widespread and showed a strong right, ipsilateral predominance (FFX analysis, Fig. 1). The most significantly activated peak (*Z* score > 8) was centered over the right M1S1 in a large voxel cluster (6567 voxels) that also encompassed the right and left SMA (Table 2). The second cortical activation focus included the right PM cortex (185 voxels, *Z* score >8). Both thalami were activated, as well as the right and left cerebellar hemispheres and the right striatum. Additional activation foci were also observed in the left insula, BA 22, BA 39, BA 43, and the right hippocampus, BA 9-44 and insula. Patient 6, who had a normal score on the Melbourne test, did not differ from other cases in terms of activation pattern. In addition, a similar activation pattern was observed in epileptic patients (patients 1, 3, and 4) and in nonepileptic

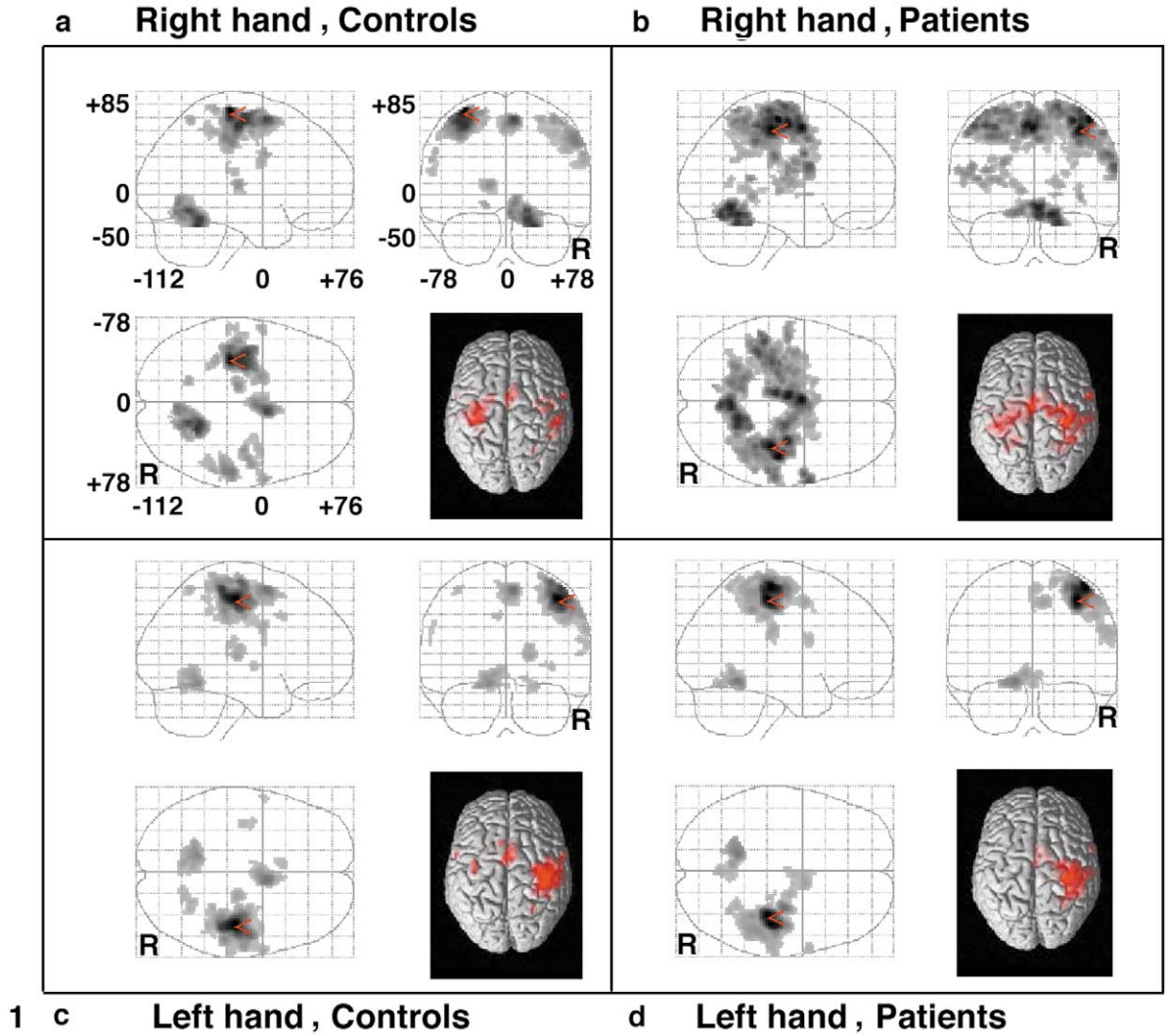

Fig. 1. Statistical parametric maps (SPM{t}) showing the brain activation during sequential finger opposition as contrasted to rest. The patterns of activation related to finger movements as contrasted to rest in controls (a–c) and patients with congenital hemiplegia (b–d) are projected onto glass brains (lateral, posterior, and superior views; R, right side of the brain). Only the voxels exceeding a threshold of $P < 0.05$ (corrected for multiple comparisons, minimal voxels cluster size, 20 voxels) are shown; the darker the voxel the stronger its statistical weight. In each SPM {t} the cursor indicates the voxel with the most significant activation (as listed in Table 2). Coordinates (a) refer to the referential defined by the atlas of Talairach and Tournoux (1988) and the MNI template (see materials and methods). In addition, each activation map is also superimposed on a surface view of a normal, spatially normalized MRI shown here for reference. (a) During finger movements of the right dominant hand, the brain activation is distributed to both hemispheres in the control group, with a contralateral left predominance. (b) During finger movements of the right paretic hand the brain activation is also distributed to both hemispheres in the patient group, but with a right ipsilateral predominance; the main activation focus is located in the right undamaged sensorimotor cortex. (c) The activation pattern for finger movements of the left nondominant hand in controls involves mainly the right contralateral hemisphere, although motor/premotor areas and SMAs

Table 2
Mean fMRI activation during sequential finger opposition in Controls and Patients

Group	Right sequential finger opposition						Left sequential finger opposition					
	Area	Coordinates			Z score	Volume (voxels)	Area	Coordinates			Z score	Volume (voxels)
		x	y	z				x	y	z		
Controls	L. M1S1	−34	−26	66	>8	1293	R. M1S1	42	−22	52	>8	2197
	R. cerebellum	22	−52	−24	>8	843	Bilateral SMA	6	2	60	>8	430
	Bilateral SMA	6	4	60	>8	423	L. cerebellum	−14	−52	−16	>8	415
	R. S1	56	−24	42	>8	450	R. thalamus	18	−20	6	>8	127
	L. thalamus	−12	−20	8	>8	119	R. cerebellum	24	−58	−18	7.50	80
	R. M1/PM	38	−14	60	>8	243	R. SPL	28	−58	60	7.31	38
	R. PM	62	2	32	>8	67	L. M1	−38	−16	60	7.02	36
	R. SPL	28	−58	60	7.63	31	R. BA 22	64	−26	16	6.89	51
	L. cerebellum	−16	−58	−8	7.62	22	L. cingulate gyrus	−6	16	38	6.62	30
	L. PM	−60	−2	28	7.05	32	R. insula	36	−8	−2	6.59	26
	L. IPL	−58	−22	18	6.43	37	R. IPL	32	−42	42	6.18	25
							L. M1/PM	−60	0	26	5.68	23
Patients	R. M1S1[a]	36	−26	52	>8	6567	R. M1S1	36	−28	52	>8	2662
	Bilateral SMA[a]	−2	−2	52	>8		L. cerebellum (+ vermis)	−14	−52	−14	>8	411
	Bilateral cerebellum (+vermis)	4	−58	−10	>8	1065	R. SMA	10	2	50	>8	275
	R. PM	64	4	22	>8	185	R. PM	60	6	20	7.15	45
	L. BA 43	−50	−12	20	>8	118						
	L. BA 22	−44	−42	12	>8	42						
	L. insula	−24	−8	26	>8	349						
	R. hippocampus	36	−40	−2	7.68	79						
	L. thalamus	−10	−20	2	7.20	66						
	R. striatum	18	2	0	7.08	21						
	R. thalamus	18	−8	8	6.86	99						
	L. BA 39	−32	−52	28	6.59	25						
	R. insula	32	−6	24	6.17	22						
	L. BA 39	−36	−58	12	6.03	20						
	R. insula	26	−12	16	6.02	23						
	R. BA 9–44	30	8	32	5.98	50						

R, right; L, left; M1, primary motor cortex (BA 4); S1, primary somatosensory cortex (BA 1, 2, 3); PM, premotor cortex (lateral BA 6); SMA, supplementary motor area (mesial BA 6); IPL, inferior parietal lobule (BA 40); SPL, superior parietal lobule (BA 7); cingulate gyrus (BA 32 and/or 24). Threshold for analysis, corrected $P < 0.05$, minimal cluster extent, 20 voxels.

[a] Belonging to the same voxel cluster.

patients (patients 2, 5, and 6) when data from these subgroups were analyzed separately.

The RFX covariate analysis did not reveal any correlation between the cerebral activation evoked by right paretic finger opposition and age (threshold for analysis, $P = 0.001$, uncorrected). There was a trend for a correlation between fMRI activation and MM score of the left nonparetic hand in a small voxel cluster centered over the right M1S1 (22 voxels; 32, −24, 44 (x, y, z coordinates); Z score = 3.81; threshold for analysis, uncorrected $P < 0.001$). In addition, the RFX analysis showed a correlation between fMRI activation and PPT score of the right paretic hand in four brain regions activated by right finger opposition (threshold for covariate analysis, uncorrected $P < 0.001$ (voxel level) and corrected $P < 0.05$ at the cluster level, Fig. 2). This correlation between residual digital dexterity and fMRI activa-

are activated bilaterally (see Table 2). The contralateral predominance during left finger opposition is more marked than that for right finger movements. (d) In the patient group, the pattern of activation related to left nonparetic finger movements is restricted to the right contralateral hemisphere. The main activation focus in this condition involves the right undamaged sensorimotor cortex with the same coordinates as during right paretic finger movements.

Fig. 2. Correlation between activation and digital dexterity in the right paretic hand. The second level (RFX) covariate analysis shows the foci with a significant correlation between fMRI activation evoked by right paretic finger movements and digital dexterity as assessed by the Purdue Pegboard Test in patients with congenital hemiplegia. SPM {t} are superimposed on axial sections of an averaged normalized MRI from the six patients (R, right side of the brain; Z refers to the slice level (mm) above the intercommissural plane). Only the voxels exceeding a threshold of $P < 0.001$ (uncorrected) and $P < 0.05$ (corrected for multiple comparisons, cluster level) are shown and the color scale codes for the T value. From left to right, a significant covariation between PPT and fMRI activation was observed in the right premotor cortex (BA 6, arrow), right superior parietal lobule (SPL, BA 7, arrow), left supplementary motor area (SMA), and right inferior parietal lobule (IPL, BA 40).

Table 3
Differential activation during sequential finger opposition between Patient and Control groups

	Differential activation with right finger movements						Differential activation with left finger movements					
	Area	Coordinates			Z score	Volume (voxels)	Area	Coordinates			Z score	Volume (voxels)
		x	y	z				x	y	z		
[Patients–Controls] (mask : Patients)	R. S1M1/PM	36	−26	50	>8	885	R. M1S1	34	−28	50	>8	247
	L. SMA	−6	−22	52	>8	571	R. M1/PM	28	−16	60	>8	47
	L. SPL	−18	−48	58	>8	88	R. SMA	12	0	50	6.45	32
	L. IPL, S1	−60	−10	18	>8	85	R. SPL	28	−48	68	6.15	21
	L. SPL	−28	−56	56	>8	44	R. IPL	54	−22	28	5.90	27
	Cerebellar vermis	2	−58	−10	7.82	58						
	L. IPL	−38	−36	54	7.38	79						
	L. Cerebellum	−14	−48	−14	7.20	22						
	L. BA 22	−44	−42	12	7.18	32						
	L. BA 37	−40	−62	8	6.90	26						
	L. Insula	−36	−10	20	6.84	31						
	L. S1, IPL	−26	−26	46	6.31	23						
[Controls–Patients] (mask : Controls)	L. M1S1	−38	−12	60	>8	291	R. M1S1	46	−16	44	>8	483
	R. SMA	6	4	60	>8	69	R. SMA[a]	6	4	60	>8	175
	L. PM	−56	0	34	>8	35	L. SMA[a]	−2	−2	64	6.30	—
							R. PM	36	−14	64	7.49	40
							L. PM	−58	0	26	7.45	86
							L. IPL/S1	−50	−24	36	7.11	41
							R. cerebellum	22	−62	−18	6.80	49

R, right; L, left; M1, primary motor cortex (BA 4); S1, primary somatosensory cortex (BA 1, 2, 3); PM, premotor cortex (lateral BA 6); SMA, supplementary motor area (mesial BA 6); IPL, inferior parietal lobule (BA 40); SPL, superior parietal lobule (BA 7). Threshold for analysis, corrected $P < 0.05$, minimal cluster extent, 20 voxels, differential activation masked by activation minus rest (see materials and methods).

[a] Belonging to the same voxel cluster.

tion involved the right IPL (33 voxels; 52, −36, 38 (*x, y, z* coordinates); *Z* score = 4.75), left SMA (154 voxels; −2, −14, 52; *Z* = 4.74), right PM cortex (38 voxels; 16, −14, 68; *Z* = 4.69), and right SPL (80 voxels; 28, −50, 66; *Z* = 4.35).

fMRI pattern during left nondominant hand movements in controls

In the control group, the performance of sequential finger opposition with the left hand resulted in a bilateral activation, though strongly lateralized to the right contralateral hemisphere (FFX analysis, Fig. 1). Significant fMRI activation was observed in the right M1S1, thalamus, SPL, BA 22, insula, IPL, and PM cortex as well as in a voxel cluster encompassing both SMAs (Table 2). Smaller activation foci were also found in the left M1, cingulate, and PM cortex as well as bilaterally in the cerebellar hemispheres (left more than right).

The RFX covariate analysis did not reveal any correlation between the cerebral activation evoked by left sequential finger opposition and age, MM score in the right fingers, or PPT score of the left hand in any activated brain area (threshold for analysis, uncorrected $P < 0.001$).

fMRI pattern during left nonparetic hand movements in hemiplegic patients

In the patient group, the activation evoked by sequential finger opposition with the left nonparetic hand was restricted to the contralateral — undamaged — hemisphere and included the right M1S1, SMA, and PM cortex (FFX analysis, Fig. 1, Table 2). The left cerebellar hemisphere and vermis were also activated. A similar activation pattern was observed in epileptic and in nonepileptic patients, as well as in patient 6.

The RFX covariate analysis did not reveal any significant correlation between fMRI activation and age, MM score in the right passive hand, or PPT score of the left nonparetic hand in any region activated by left sequential finger opposition (threshold for analysis, uncorrected $P < 0.001$).

Differential activation in patients and controls during right hand movements

In FFX analysis, the [Patients–Controls] contrast showed a stronger activation in the patient group than in the control group in a large voxel cluster encompassing the right M1S1 and PM cortex, as well as in the left SMA (Table 3). There were also additional activation foci on the left side, i.e., IPL, SPL, insula, and BA 37, that were more activated in patients

than in controls. The left cerebellum and the vermis were also more significantly activated in the patient group. The second level (RFX) analysis showed a similar pattern, though to a nonsignificant level ($P = 0.001$, uncorrected). In particular, the fMRI activation during right finger movements was stronger in the patient group than in the control group in the left SMA (64 voxels; −8, −16, 54; Z score = 4.28) and the right precentral gyrus (M1/PM, 27 voxels; 24, −18, 64; $Z = 3.77$).

Conversely and as revealed by the [Controls–Patients] contrast in FFX analysis, the left M1S1 and PM cortex and the right SMA were more strongly activated in the control than in the patient group (Table 3). These small foci were not observed in the RFX analysis ($P = 0.001$, uncorrected), maybe due to the reduced number of subjects.

Differential activation in patients and controls during left hand movements

In FFX analysis, the [Patients–Controls] contrast showed that several brain areas, all located in the right, undamaged hemisphere, were more significantly activated in the patient group than in the control group during left sequential finger opposition. These foci encompassed the right M1S1, PM cortex, SMA, SPL, and IPL (Table 3). The RFX analysis failed to show a significant differential activation between the patient and control groups ($P = 0.001$, uncorrected).

The inverse contrast [Controls–Patients] revealed that bilateral regions were more activated in the control than in the patient group during left finger movements. These regions included a part of the right M1S1 (Table 3), which was located more laterally and anterior to the M1S1 region shown by the [Patients–Controls] contrast. Stronger activation in the control group was also found in the right PM cortex (more laterally than in the reverse contrast), in the right and left SMA, in the left PM, IPL/S1, and in the right cerebellum. The RFX analysis failed to show a significant differential activation between the patient and control groups ($P = 0.001$, uncorrected).

Discussion

The fMRI activation correlating with movements of the right fingers was bilaterally distributed in both the hemiplegic patient and control groups, but a strong right ipsilateral predominance was observed in the patient group, in opposition to the leftward contralateral predominance disclosed in the control group. This may indicate a relatively stronger implication of the undamaged hemisphere during task performance with the ipsilateral paretic hand, further supported by a covariation between this activation and the residual digital dexterity (PPT). During left finger movements, the bilateral fMRI activation was strongly asymmetric in favor of the right contralateral hemisphere in the control group, whereas an exclusive activation of the right undamaged hemisphere was observed in the patient group.

Methodological considerations and limitations

In the present study, a self-paced sequential finger opposition was chosen to uncover the cerebral activation related to the execution of discrete finger movements with either hand at a preferred and spontaneous rate. One potential problem in using a self-paced movement is that presumably the control group produced a larger number of movements in each epoch than did the patient group. One could have expected that this would lead to larger activation of the contralateral hemisphere in the control group. However, a large number of contralateral activation foci was observed in the patient group, including nonmotor areas in the damaged hemisphere. Moreover, despite the presence of spasticity, cocontractions, and motor impairment, the patients were able to achieve the task with the paretic fingers, even if they had to make greater efforts, especially to maintain their performance throughout the fMRI session. This may have resulted in the recruitment of additional areas in congenital hemiplegic patients (Staudt et al., 2002). Therefore, although the task difficulty was obviously different for patients and controls, there was no attempt to correct the task performance for rhythm or subjective effort that could influence the activation patterns (Sadato et al., 1996, 1997a; Jäncke et al., 1998) and accordingly, the widespread activation including both hemispheres in the patient group may be related, at least partly, to the nonspecific recruitment of additional areas during the performance of more demanding movements in patients compared to control subjects.

The Purdue Pegboard Test is considered a reliable quantitative measure of digital dexterity (Mathiowetz et al., 1986; Backman et al., 1992; Smith et al., 2000). The PPT and the sequential finger opposition task are different tasks and are supposed to involve partly different cortico-subcortical circuits. However, both tasks require the performance of complex, finely tuned, and independent finger movements that are known to engage a common network of premotor and primary sensorimotor areas, especially M1 and its corticospinal projections, at least in normal subjects. For this reason, the PPT score was used as a covariate in statistical analysis to unveil the brain areas wherein the fMRI activation elicited by unilateral finger movements was positively correlated with digital dexterity.

The isometric half-flexion of the elbow during finger movement required the contraction of proximal muscles and this could have contributed to the bilateral activation of sensorimotor areas (Nirkko et al., 2001) in addition to that induced by unimanual sequential finger opposition (Kim et al., 1993; Sadato et al., 1996). However, there was no obvious difference between patients and controls in the elbow flexion during the task. Since the passive hand was continuously restrained in patients to reduce motion artifacts due to mirror movements, we cannot definitely rule out

that some increased somatosensory input from the passive restrained hand resulted in additional activation.

The fMRI activation patterns reported previously during cognitive, motor, or sensory tasks in children older than 5 years of age elicit patterns of activation similar to those in adults with only minor differences (Gaillard et al., 2001). In the present study, dealing with subjects aged from 9 to 17 years, the RFX covariate analysis failed to show any correlation between fMRI activation and age. Moreover, since patients and control subjects were matched for age, these developmental effects are unlikely to account for the differences between groups.

Finally, the number of subjects in RFX analysis was too small to get significant results in order to make inferences at the level of the population (Holmes and Friston, 1998). For this reason, the conclusions of the present FFX analysis are mostly restricted to the subjects under study.

fMRI activation evoked by right sequential finger opposition

In the control children, the fMRI activation related to finger movements of the right dominant hand was distributed in both hemispheres. The contralateral left hemisphere was more extensively and more significantly activated, as repeatedly described in previous studies carried out in right-handed adults (Kim et al., 1993; Kawashima et al., 1993; Catalan et al., 1998). By contrast, although the fMRI activation was also bilaterally distributed in the patient group, by far the most significant and largest activation foci observed during movement of the right paretic fingers were located in the ipsilateral undamaged hemisphere. This is in accordance with previous studies (Cao et al., 1994; Nirkko et al., 1997; Macdonell et al., 1999; Thickbroom et al., 2001; Staudt et al., 2001; Johansen-Berg et al., 2002a). Moreover, the present study disclosed a correlation between the residual digital dexterity of the paretic hand and the intensity of the activation in the premotor and parietal cortices of the undamaged hemisphere, as indicated by the covariate analysis. It is thus sensible to hypothesize that the undamaged hemisphere played a significant role in functional recovery in our patients. On the one hand, a recruitment of the ipsilateral premotor cortex has been observed in adult stroke patients studied by fMRI and using TMS as a temporary interference technique (Johansen-Berg et al., 2002a), especially in the more impaired patients. On the other hand, in recent fMRI studies carried out in right-handed adults, the ipsilateral intraparietal cortex was involved in the sensorimotor integration required for the control of fine fingertip forces during precision grip with the right dominant hand (Ehrsson et al., 2001). Accordingly, it could be hypothesized that the ipsilateral intraparietal cortex may play a role during the realization of relatively independent finger movements and that, in patients with congenital hemiplegia, the premotor and the parietal cortices of the undamaged hemisphere could significantly contribute to functional recovery.

Alternatively, the activation of the undamaged hemisphere, especially in M1S1, could also be related to the motor output resulting in mirror movements in the nonparetic hand (Staudt et al., 2002) or to increased somatosensory inputs due to its restrain during the fMRI procedure. The activation of M1S1 in the undamaged hemisphere may also be due to an imbalance between the transcallosal inhibitory connections as suggested in adult stroke patients (Weiller et al., 1992; Boroojerdi et al., 1996). In the present study, the most significant and largest activation foci were centered over almost identical coordinates in M1S1 and PM cortex of the undamaged hemisphere during task performance with either the right or left fingers in the patient group. This brings support to the hypothesis of MM-related activation. The RFX covariate analysis also disclosed a trend for a correlation between MM in the nonparetic passive hand and the M1S1 activation observed in the undamaged hemisphere during paretic finger movements. For these reasons, it is likely that a part of the ipsilateral M1S1 activation during paretic finger movements could be ascribed to MM in the passive nonparetic hand in addition to interhemispheric transfer of function (Cao et al., 1994; Nirkko et al., 1997; Macdonell et al., 1999; Thickbroom et al., 2001; Staudt et al., 2002). This suggests, but does not prove, that a part of the M1S1 activation in the undamaged hemisphere may be due to the recruitment of crossed corticospinal projections leading to MM and/or to sensory feedback from the involuntary mirroring hand (Krams et al., 1997) rather than to a lack of transcallosal inhibition.

In the damaged hemisphere, the premotor and parietal areas can also underlie functional recovery after an injury of M1 or of its corticospinal projections (Chollet et al., 1991; Cao et al., 1994; Staudt et al., 2001; Johansen-Berg et al., 2002b). Accordingly, the widespread activation of the left damaged hemisphere in the present study may be related to compensatory recruitment of the SMA and parietal areas of the damaged hemisphere, as previously suggested in congenital hemiplegics and adult stroke patients (Cao et al., 1994; Johansen-Berg et al., 2002b). The gradient of interhemispheric transfer, ranging from partial to complete, might depend on the location and extent of injury (Staudt et al., 2002) as well as on other factors, such as the timing of insult relative to the cerebral development (Carr et al., 1993; Holloway et al., 2000; Staudt et al., 2002). It has been suggested that somatosensory processes remained preferentially located in the affected hemisphere, whereas the control of the paretic hand movements could be relocated in the undamaged hemisphere in patients with congenital hemiplegia (Thickbroom et al., 2001). If such an interhemispheric dissociation between motor and somatosensory processes was present in our patients, some part of the fMRI activation disclosed in the affected hemisphere especially in S1 and parietal areas, could have resulted from somatosensory input from the paretic hand during movement. However, other

studies indicated that both motor and somatosensory functions can shift toward the undamaged hemisphere after early brain injury (Lewine et al., 1994; Macdonell et al., 1999; Chu et al., 2000; Holloway et al., 2000). In addition, there was a more diffuse activation of both hemispheres in patients than in controls, including many nonmotor brain areas in the damaged hemisphere, as also reflected by the differential activation between patient and control groups. Part of this widespread activation including both hemispheres in the patient group could be related, at least partly, to the nonspecific recruitment of additional areas due to the difficulty of the task, which was larger for hemiplegic patients than for controls. In the present study, the SMA was the only area of the damaged hemisphere wherein the fMRI activation correlated positively with the residual digital dexterity of the paretic hand. Interestingly, this is consistent with the repeatedly reported association of SMA activation with complexity of movement and responsiveness to internal cueing of movement (Catalan et al., 1998, and references therein). Finally, since the cerebral lesions were not identically located in our patients and since the clinical deficit was not uniform, it is likely that such a trend toward an increased reliance over the undamaged hemisphere for sensorimotor processing was not uniformly distributed across the patients. This may further account for the more widespread bilateral activation in the patient group compared to the controls.

fMRI activation evoked by left sequential finger opposition

In the control group, sequential finger opposition with the left nondominant hand resulted in bilateral activation, albeit with a smaller volume of activation in the ipsilateral hemisphere than did right finger movements. This finding stands in contrast with the currently admitted notion that the left dominant hemisphere is much more involved than the right nondominant hemisphere in the control of the ipsilateral upper limb movements in normal right-handed subjects (Kawashima et al., 1993; Kim et al., 1993; Li et al., 1996; Baraldi et al., 1999). In our control group, there was no obvious difference in fMRI task performance by either hand nor in digital dexterity as assessed by the PPT test. Additional activation studies in a larger group of children are needed to infer the present results at the level of the population. Nevertheless, it is tempting to suggest that the bias of ipsilateral motor control in favor of the left dominant hemisphere in right-handed adults could not be the rule in children and that maturation effects could account for this subtle difference. Maturation effects also account for the ability to shift hand dominance and for mirror movements that are observed in children until the age of 10 years (Woods and Teuber, 1978).

In contrast with the bilateral activation observed in controls, sequential finger opposition with the left nonparetic hand resulted in an exclusive activation of the contralateral undamaged hemisphere in hemiplegic patients. Previous studies with functional imaging brought discrepant results regarding the activation pattern evoked by movements of the nonparetic hand in adult or pediatric hemiparetic patients. A lack of difference between patients and control subjects has been reported (Chollet et al., 1991; Sabatini et al., 1994; Cramer et al., 1997; Cao et al., 1998; Müller et al., 1998b), as well as a relative overactivation of the unaffected hemisphere in the hemiparetic group (Marshall et al., 2000; Staudt et al., 2002). The present results indicate the absence of significant involvement of the damaged hemisphere in the execution of ipsilateral movements with the nonparetic fingers in children with congenital hemiplegia. Subtle but indubitable functional impairment of the nonparetic hand has been repeatedly reported both in adult stroke patients and in congenital hemiplegics (Colebatch and Gandevia, 1989; Jones et al., 1989; Gordon et al., 1999; Marshall et al., 2000; Duque et al., 2003). The present study is in accordance with these observations if one admits that the best performance of the patients, using their nonparetic hand at the Purdue Pegboard Test, was slightly inferior to that obtained by the control subjects with their dominant hand. Mercuri et al. (1999) suggested that the impairment of the nonparetic upper limb in congenital hemiplegics may be explained by the frequent occurrence of bilateral parenchymal lesions. However, these functional deficits are also consistent with the fact that each cerebral hemisphere is at least partly involved in the control of the ipsilateral upper limb (Kim et al., 1993; Chen et al., 1997; Cramer et al., 1999; Nirkko et al., 2001). Therefore, it is likely that the functional integrity of both hemispheres is required for the performance of highly skilled movements (Gordon et al., 1999). We hypothesize that a part of the subtle impairment observed in the nonparetic hand could be reflected by the unilateral fMRI activation pattern, restricted to the undamaged hemisphere and related to an excessive lateralization of the motor control.

Conclusions

Although these findings may not be applicable to all types of congenital hemiplegia, the present observations suggest an overall increased reliance upon the undamaged hemisphere during the realization of independent finger movements with either the paretic or nonparetic hand. This indicates a partial interhemispheric transfer of the motor function in hemiplegic children, with the undamaged hemisphere having taken over the control of the ipsilateral paretic hand after early brain injury. Additional studies would investigate further whether the activation pattern abnormally confined to the undamaged hemisphere is related to the subtle impairment observed in the nonparetic upper limb of patients with congenital hemiplegia.

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References

Aicardi, J., Bax, M., 1998. Cerebral palsy, in: Aicardi, J., Bax, M., Gillberg, C., Ogier, H. (Eds.), Diseases of the Nervous System in Childhood, 2nd ed. MacKeith Press, London, UK, pp. 210–239.

Ashworth, B., 1964. Preliminary trial of carisoprodal in multiple sclerosis. Practitioner 192, 540–542.

Backman, C., Cork, S., Gibson, D., Parson, J., 1992. Assessment of hand function: the relation between pegboard dexterity and applied dexterity. Can. J. Occup. Ther. 59, 208–213.

Baraldi, P., Porro, C.A., Serafini, M., Pagnoni, G., Murari, C., Corazza, R., Nichelli, P., 1999. Bilateral representation of sequential finger movements in human cortical areas. Neurosci. Lett. 269, 95–98.

Boroojerdi, B., Diefenbach, K., Ferbert, A., 1996. Transcallosal inhibition in cortical and subcortical cerebral vascular lesions. J. Neurol. Sci. 144, 160–170.

Brett, M., Leff, A.P., Rorden, C., Ashburner, J., 2001. Spatial normalization of brain images with focal lesions using cost function masking. NeuroImage 14, 486–500.

Brunnstrom, S., 1966. Motor testing procedures in hemiplegia: based on sequential recovery stages. Phys. Ther. 46, 357–375.

Cao, Y., Vikingstad, E.M., Huttenlocher, P.R., Towle, V.L., Levin, D.N., 1994. Functional magnetic resonance studies of the reorganization of the human hand sensorimotor area after unilateral brain injury in the perinatal period. Proc. Natl. Acad. Sci. USA 91, 9612–9616.

Cao, Y., D'Olhaberriague, L., Vikingstad, E.M., Levine, S.R., Welch, K.M., 1998. Pilot study of functional MRI to assess cerebral activation of motor function after poststroke hemiparesis. Stroke 29, 112–122.

Carr, L.J., Harrison, L.M., Evans, A.L., Stephens, A.J., 1993. Patterns of central motor reorganization in hemiplegic cerebral palsy. Brain 116, 1223–1247.

Catalan, M.J., Honda, M., Weeks, R.A., Cohen, L.G., Hallett, M., 1998. The functional neuroanatomy of simple and complex sequential finger movements: a PET study. Brain 121, 253–264.

Chen, R., Gerloff, C., Hallett, M., Cohen, L.G., 1997. Involvement of the ipsilateral motor cortex in finger movements of different complexities. Ann. Neurol. 41, 247–254.

Chollet, F., DiPiero, V., Wise, R.J.S., Brooks, D.J., Dolan, R.J., Frackowiak, R.S.J., 1991. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann. Neurol. 29, 63–71.

Chu, D., Huttenlocher, P.R., Levin, D.N., Towle, V.L., 2000. Reorganization of the hand somatosensory cortex following perinatal unilateral brain injury. Neuropediatrics 31, 63–69.

Claeys, V., Deonna, T., Chrzanowski, R., 1983. Congenital hemiparesis: the spectrum of lesions. A clinical and computerized tomographic study of 37 cases. Helv. Paediatr. Acta 38, 439–455.

Colebatch, J.G., Gandevia, S.C., 1989. The distribution of muscular weakness in upper limb motor neuron lesions affecting the arm. Brain 112, 749–763.

Cramer, S.C., Nelles, G., Benson, R.R., Kaplan, J.D., Parker, R.A., Kwong, K.K., Kennedy, D.N., Finkelstein, S.P., Rosen, B.R., 1997. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke 28, 2518–2527.

Cramer, S.C., Finkelstein, S.P., Schaechter, J.D., Bush, G., Rosen, B.R., 1999. Distinct regions of motor cortex control ipsilateral and contralateral finger movements. J. Neurophysiol. 81, 383–387.

Duque, J., Thonnard, J.L., Vandermeeren, Y., Sebire, G., Cosnard, G., Olivier, E., 2003. Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia. Brain 126, 732–747.

Ehrsson, H.H., Fagergren, A., Forssberg, H., 2001. Differential frontoparietal activation depending on force used in a precision grip task: an fMRI study. J. Neurophysiol. 85, 2613–2623.

Eliasson, A.C., Gordon, M., 2000. Impaired force coordination during object release in children with hemiplegic cerebral palsy. Dev. Med. Child Neurol. 42, 228–234.

Forssberg, H., Eliasson, A.V., Redon-Zoitenn, C., Mercuri, E., Dubowitz, L., 1999. Impaired grip-lift synergy in children with unilateral brain lesions. Brain 122, 1157–1168.

Friston, K.J., Ashburner, J., Poline, J.-B., Fritz, C.D., Heather, J.D., Frackowiak, R.S.J., 1995a. Spatial registration and normalization of images. Hum. Brain Mapp. 2, 165–189.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-B., Frith, C.D., Frackowiak, R.S.J., 1995b. Statistical parametric maps in functional imaging: A general approach. Hum. Brain Mapp. 2, 189–210.

Gaillard, W.D., Grandin, C.B., Xu, B., 2001. Developmental aspects of pediatric fMRI: considerations for image acquisition, analysis and interpretation. NeuroImage 13, 239–249.

Gordon, A.M., Charles, J., Duff, S., 1999. Fingertip forces during objects manipulation with hemiplegic cerebral palsy. II: bilateral coordination. Dev. Med. Child Neurol. 41, 176–185.

Holloway, V., Gadian, D.G., Vargha-Khadem, F., Porter, D.A., Boyd, S.G., Connelly, A., 2000. The reorganization of sensorimotor function in children after hemispherectomy. A functional MRI and somatosensory evoked potential study. Brain 123, 2432–2444.

Holmes, A.P., Friston, K.J., 1998. Generalizability, random effects, and population inference. NeuroImage 7, S754.

Jäncke, L., Peters, M., Schlaug, G., Posse, S., Steinmetz, H., Müller-Gärtner, H.W., 1998. Differential magnetic resonance signal change in human sensorimotor cortex to finger movements of different rate of the dominant and subdominant hand. Cogn. Brain Res. 6, 279–284.

Johansen-Berg, H., Rushworth, M.F., Bogdanovic, M.D., Kischka, U., Wimalaratna, S., Matthews, P.M., 2002a. The role of ipsilateral premotor cortex in hand movement after stroke. Proc. Natl. Acad. Sci. USA 99, 14518–14523.

Johansen-Berg, H., Dawes, H., Guy, C., Smith, S.M., Wade, D.T., Matthews, P.M., 2002b. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain 125, 2731–2742.

Jones, R.J., Donaldson, I.M., Parkin, P.J., 1989. Impairment and recovery of ipsilateral sensory-motor function following unilateral cerebral infraction. Brain 112, 113–132.

Kawashima, R., Yamada, K., Kinomura, S., Yamaguchi, T., Matsui, H., Yoshioka, S., Fukuda, H., 1993. Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movement. Brain Res. 623, 33–40.

Keith, R.A., Granger, C.V., Hamilton, B.B., Sherwin, F.S., 1987. The functional independence measure: a new tool for rehabilitation. Adv. Clin. Rehabil. 1, 6–18.

Kim, S.G., Ashe, J., Hendrich, K., Ellermann, J.M., Merkle, H., Ugurbil, K., Georgeopoulos, A.P., 1993. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science 261, 615–617.

Krams, M., Quinton, R., Mayston, M.J., Harrison, L.M., Dolan, R.J., Bouloux, P.M., Stephens, J.A., Frackowiak, R.S.J., Passingham, R.E., 1997. Mirror movements in X- linked Kallmann's syndrome. II. A PET study. Brain 120, 1217–1228.

Lawrence, D.G., Hopkins, D.A., 1976. The development of motor control in the rhesus monkey: evidence concerning the role of corticomotoneuronal connections. Brain 99, 235–254.

Lewine, J.D., Astur, R.S., Davis, L.E., Knight, J.E., Maclin, E.L., Orrison, W.W., 1994. Cortical organization in adulthood is modified by neonatal infarct: a case study. Radiology 190, 93–96.

Li, A., Yetkin, Z., Cox, R., Haughton, V.M., 1996. Ipsilateral hemisphere activation during motor and sensory tasks. Am. J. Neuroradiol. 17, 651–655.

Macdonell, R.A.L., Jackson, G.D., Curatolo, J.M., Abbott, D.F., Berkovic, S.F., Carey, L.M., Syngeniotin, A., Fabinyi, G.C., Scheffer, I.E., 1999. Motor cortex localization using functional MRI and transcranial magnetic stimulation. Neurology 53, 1462–1467.

Marshall, R.S., Perera, G.M., Lazar, R.M., Krakauer, J.W., Constantine, R.C., DeLaPaz, R.L., 2000. Evolution of cortical activation during recovery from corticospinal tract infarction. Stroke 31, 656–661.

Mathiowetz, V., Rogers, S.L., Dowe-Keval, M., Donahoe, L., Rennells, C., 1986. The Purdue Pegboard: norms for 14- to 19-years-old. Am. J. Occup. Ther. 40, 174–179.

Mayston, M.J., Harrison, L.M., Quinton, R., Stephens, J.A., Krams, M., Bouloux, P.M., 1997. Mirror movements in X-linked Kallmann's syndrome. I. A neurophysiological study. Brain 120, 1199–1216.

Mercuri, E., Jongmans, M., Bouza, H., Haataja, L., Rutherford, M., Henderson, S., Dubowitz, L., 1999. Congenital hemiplegia in children at school age: assessment of hand function in the non hemiplegic hand and correlation with MRI. Neuropediatrics 30, 8–13.

Michel, C., Sibomana, M., Bodart, J.-M., Grandin, C., Coppens, A., Bol, A., De Volder, A.G., Warscotte, V., Thiran, J.P., Macq, B., 1995. Interactive delineation of brain sulci and their merging into functional PET images, in: Moonier, P.A. (Ed.), Proceedings of IEEE Medical Imaging Conference, Vol. 3. IEEE Service Center, San Francisco, pp. 1480–1484.

Müller, R.A., Rothermel, R.D., Behen, M.E., Muzik, O., Mangner, T.J., Chugani, H.T., 1998a. Differential patterns of language and motor reorganization following early left hemisphere lesion. Arch. Neurol. 55, 1113–1119.

Müller, R.A., Watson, C.E., Muzik, O., Chakraborty, P.K., Chugani, H.T., 1998b. Motor organization after early middle cerebral artery stroke: a PET study. Pediatric Neurol. 19, 294–298.

Nirkko, A.C., Rösler, K.M., Ozboda, C., Heid, O., Schroth, G., Hess, C.W., 1997. Human cortical plasticity: functional recovery with mirror movements. Neurology 48, 1090–1093.

Nirkko, A.C., Ozboda, C., Redmond, S.M., Bürki, M., Schroth, G., Hess, C.W., Wiesendanger, M., 2001. Different ipsilateral representations for distal and proximal movements in the sensorimotor cortex: activation and deactivation patterns. NeuroImage 13, 825–835.

Oldfield, R.C., 1971. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9, 97–113.

Passingham, R.E., Perry, V.H., Wilkinson, F., 1983. The long-term effects of removal of sensorimotor cortex in infant and adult rhesus monkeys. Brain 106, 675–705.

Payne, B.R., Lomber, S.G., 2001. Reconstructing functional systems after lesions of cerebral cortex. Nature Rev. Neurosci. 2, 911–919.

Pietrzyk, U., Herholz, K., Fink, G., Jacobs, A., Mielke, R., Slansky, I., Würker, M., Heiss, W.D., 1994. An interactive technique for three-dimensional image registration: validation for PET, SPECT, MRI, and CT brain studies. J. Nucl. Med. 35, 2011–2018.

Randall, M., Carlin, J.B., Chondros, P., Reddihough, D., 2001. Reliability of the Melbourne assessment of unilateral upper limb function. Dev. Med. Child Neurol. 43, 761–767.

Rouiller, E.M., Yu, X.H., Moret, V., Tempini, A., Wiesendanger, M., Liang, F., 1998. Dexterity in adult monkeys following early lesion of the motor cortical hand area: the role of cortex adjacent to the lesion. Eur. J. Neurosci. 10, 729–740.

Sabatini, U., Toni, D., Pantano, P., Brughitta, G., Padovani, A., Bozzao, L., Lenzi, G.L., 1994. Motor recovery after early brain damage: a case of brain plasticity. Stroke 25, 514–517.

Sadato, N., Campbell, G., Ibanez, V., Deiber, M.P., Hallett, M., 1996. Complexity affects regional cerebral blood flow change during sequential finger movements. J. Neurosci. 16, 2693–2700.

Smith, Y.A., Hong, E.S., Presson, C., 2000. Normative and validation studies of the Nine-hole Peg Test with children. Percept. Motor Skills 90, 823–843.

Staudt, M., Pieper, T., Grodd, W., Winkler, P., Hothausen, H., Krägeloh-Mann, I., 2001. Functional MRI in a 6-year-old boy with unilateral cortical malformation: concordant representation of both hands in the unaffected hemisphere. Neuropediatrics 32, 159–161.

Staudt, M., Grodd, W., Gerloff, C., Erb, M., Stitz, J., Krägeloh-Mann, I., 2002. Two types of ipsilateral reorganization in congenital hemiparesis. A TMS and fMRI study. Brain 125, 2222–2237.

Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.

Thickbroom, G.W., Byrnes, M.L., Archer, S.A., Nagarajan, L., Mastaglia, F.L., 2001. Differences in sensory and motor cortical organization following brain injury early in life. Ann. Neurol. 49, 320–327.

Vandermeeren, Y., De Volder, A.G., Bastings, E., Thonnard, J.L., Duqué, J., Grandin, C., Sébire, G., Olivier, E., 2002a. Functional relevance of motor cortex reorganisation in a child with unilateral schizencephaly. Neuroreport 13, 1821–1824.

Vandermeeren, Y., Olivier, E., Sébire, G., Cosnard, G., Bol, A., Sibomana, M., Michel, C., De Volder, A.G., 2002b. Increased FDG uptake in the ipsilesional sensorimotor cortex in congenital hemiplegia. NeuroImage 15, 949–960.

Weiller, C., Chollet, F., Friston, K.J., Wise, R.J.S., Frackowiak, R.S.J., 1992. Functional reorganization of the brain in recovery from striatocapsular infarction in man. Ann. Neurol. 31, 463–472.

Woods, B.T., Teuber, H.L., 1978. Mirror movements after childhood hemiparesis. Neurology 28, 1152–1158.