Two types of ipsilateral reorganization in congenital hemiparesis  
A TMS and fMRI study

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Summary
Reorganization after early brain injuries is not only determined by the maturational stage of the CNS at the time of the insult (timing), but also by the structural properties, location and extent of the lesion. This study addresses the impact of different lesion extents on the type of reorganization induced in a cohort of patients with lesions of uniform structure and location (unilateral periventricular defects) and similar timing (early third trimester of pregnancy). Twelve young adult patients with congenital hemiparesis and 10 age-matched controls were studied. The severity of structural damage to hand motor projections of the cortico-spinal tract was assessed on semi-coronal MRI reconstructions along anatomical landmarks of cortico-spinal tract somatotopy. The functional integrity of these crossed cortico-spinal projections in the affected hemisphere, as well as the presence of any abnormal ipsilateral projections to the paretic hand, was examined by transcranial magnetic stimulation (TMS). Cortical activation during simple voluntary hand movements was studied by functional MRI (fMRI). Patients with small lesions (SL; n = 4) and only mild hand motor impairment possessed intact crossed cortico-spinal projections to the paretic hand, whereas no motor response could be elicited by TMS of the affected hemisphere in those with large lesions (LL; n = 6) and more severe hand motor impairment. Evidence for compensatory recruitment of the unaffected hemisphere was found in both subgroups. In the SL group, fMRI demonstrated ipsilateral activation of premotor areas, without any abnormal projections to the paretic hand originating from these sites. In the LL group, such abnormal ipsilateral projections to the paretic hand were indeed found, and fMRI confirmed cortical activation of an abnormal ipsilateral hand motor representation in the primary sensorimotor region of the unaffected hemisphere. Two patients with intermediate-sized lesions presented combined features of both groups (SL, LL). In conclusion, this study provides evidence that the type of cortico-spinal reorganization depends on the extent of the brain lesion. We propose that involvement of the ipsilateral hemisphere can be (i) of the premotor type, i.e. without ipsilateral motor projections but with significant activation of ipsilateral premotor areas, or (ii) of the primary motor type, i.e. with abnormal ipsilateral cortico-spinal projections to the paretic hand.

Keywords: early brain lesions; reorganization; sensorimotor; periventricular; cortico-spinal tract

Abbreviations: fMRI = functional magnetic resonance imaging; LL = large lesions; MEP = motor evoked potential; MM = mirror movements; MT = motor threshold; OP = optimal point; PCA = post-conceptional age; SL = small lesions; TMS = transcranial magnetic stimulation

Introduction
The compensatory capabilities of the immature nervous system following focal brain injury are superior to those of the adult brain. This observation is known as the Kennard principle, after a study of recovery after experimental lesions to the motor cortex in monkeys (Kennard, 1936). For sensorimotor reorganization following early unilateral brain lesions in humans, enhanced participation of the unaffected hemisphere has been identified as an important ingredient. In

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neurophysiological investigations, one of the most frequent and consistent observations has been the detection of abnormal motor projections originating from the unaffected hemisphere and projecting ipsilaterally to the paretic side of the body (Benecke et al., 1991; Farmer et al., 1991; Carr et al., 1993; Maegaki et al., 1997; Nezu et al., 1999). Such projections have, however, not been found in all affected patients; furthermore, studies dealing with the cortical origin of these projections and their conduction velocities have reported diverging results for different subsets of patients (Benecke et al., 1991; Farmer et al., 1991; Carr et al., 1993; Maegaki et al., 1995, 1997; Nirkko et al., 1997; Watson and Colebatch, 1997; Macdonell et al., 1999; Nezu et al., 1999; Thickbroom et al., 2001). Functional imaging examinations also reported considerable variability of cortical activation in the unaffected hemisphere during movement of the affected hand including primary motor, premotor and also parietal areas (Cao et al., 1994; Nirkko et al., 1997; Müller et al., 1997b, 1998a, b; Macdonell et al., 1999; Bernasco et al., 2000; Staudt et al., 2001; Thickbroom et al., 2001).

Among the many factors that have been shown or suspected to influence this process, four seem to be of particular importance: (i) structural properties, (ii) location, (iii) extent of the lesion and (iv) the maturational stage of the nervous system at the time of the insult (Woods and Teuber, 1978). In patients without any visible lesions, grades 3–4 in the criteria proposed by Woods and Teuber, 1978; Carr et al., 1993; Maegaki et al., 1997; Müller et al., 1997b; Nezu et al., 1999; Thickbroom et al., 2001). Little is known, however, about the different influences these factors have on sensorimotor reorganization, mostly because previous studies often included subjects with several types of underlying pathologies and even patients from whom no structural imaging information was available.

For the present study, we recruited a sample more homogeneous than those of prior investigations, and included only patients suffering from congenital hemiparesis due to unilateral defects in the periventricular white matter. Within these inclusion criteria, we could keep the factors ‘structural properties’ and ‘location’ relatively constant. Furthermore, this type of lesion can be assigned to the early third trimester of pregnancy (24–36 weeks post-conceptual age (PCA)), a time when such insults occur either as complications of premature birth or as, often unnoticed, prenatally acquired lesions in term-born children (Krägeloh-Mann et al., 1995; Volpe, 1995). This sample could, therefore, be considered homogeneous in terms of the location, structure and timing of the lesions. Thus, it became possible to investigate the effect of different lesion extents as the remaining variable factor in the present study.

Note that the term ‘reorganization’ can, strictly speaking, only be applied to changes in organization that occur after some type of regular organization has already been established. This might not be the case in every patient with a very early brain lesion, where CNS organization might have been abnormal from the start. For the sake of readability, we will, nevertheless, use this term in a broader sense to indicate ‘lesion-induced deviations from normal organization’.

**Patients and methods**

Twelve patients with congenital hemiparesis (6 females, 6 males; age range = 16–25 years; mean age = 20.2 years) participated in the study. The demographic data as well as the perinatal and perinatal histories are summarized in Table 1. Structural MRI had been performed prior to this study in all patients and had revealed unilateral lesions in the periventricular white matter. To ensure good compliance for the functional MRI (fMRI) experiments, we recruited only patients without cognitive impairment and over 16 years of age. This age limitation has the additional advantage that the age-dependency of paediatric transcranial magnetic stimulation (TMS) results is no longer relevant (Eyre et al., 2001). Two patients had histories of seizures: Patient 9 had experienced a single febrile seizure during a measles infection and Patient 11 had suffered a few epileptic seizures several years before the onset of the study and was still on carbamazepine.

All 12 patients underwent fMRI, whereas TMS could be performed in only nine as two were not willing to participate in this part of the study (Patients 7 and 11) and one woman was pregnant at the time of the planned TMS examination (Patient 12). The control group consisted of 10 healthy, adult righthanders (6 females, 4 males; age range = 19–33 years; mean age = 29.4 years; fMRI in six; TMS in seven). Informed written consent and approval from the Ethik Kommission der Medizinische Fakultät, Eberhard-Karls-Universität, Tübingen, were obtained on the condition that, in epileptic subjects, TMS was only used when no seizure had occurred for at least two years prior to the examination.

**Clinical assessment**

A standardized, video-documented neurological examination was performed in all patients. Paretic hand function was graded with the sequential finger opposition task as: 1 = normal performance; 2 = slow and/or incomplete performance; 3 = inability to perform any independent finger movements (Staudt et al., 2000). Even the most severely affected patients could, however, use their paretic hands for global grasping; hence, according to the classification by Claeyss and colleagues (Claeyss et al., 1983), none of them suffered from severe hemiparesis, i.e. a total lack of voluntary prehension.

Associated involuntary movements of the opposite hand during voluntary unimanual movements were assessed during repetitive fist clenching, repetitive index finger-to-thumb opposition and sequential finger-to-thumb opposition. The term ‘mirror movements’ (MM) was only used when such involuntary finger movements were reproducible, phasic and exceeded an amplitude of 10 mm at the fingertips. It did not include tonic contractions without phasic components or erratic twitches of single fingers. This definition corresponds to grades 3–4 in the criteria proposed by Woods and Teuber (Woods and Teuber, 1978). In patients without any visible
contractions of the opposite hand, the absence of subclinical motor activity was documented by surface EMG recordings from electrodes placed over the patients’ forearm extensor muscles during repetitive opening and closing of the other hand (equivalent to the fMRI task, see below).

TMS
TMS was performed using a Magstim 200 Stimulator (The Magstim Company Ltd, Whitland, Wales, UK) equipped with a focal 2 × 70 mm figure-eight coil and a Nicolet Viking IV D EMG unit (Nicolet Biomedical Instruments, Madison, WI, USA) (digitization rate = 10 kHz, high-pass filter = 100 Hz, low-pass filter = 5 kHz). Motor evoked potentials (MEPs) were recorded simultaneously from both forearms using surface EMG electrodes attached over the patients’ finger extensor muscles (M. extensor digitorum), 5 cm apart. We chose this location in order to correspond as closely as possible with our fMRI task of repetitive opening and closing of the hand, rather than to record from intrinsic hand muscles (Carr et al., 1993; Maegaki et al., 1995, 1997; Nirkko et al., 1997; Macdonell et al., 1999; Nezu et al., 1999; Thickbroom et al., 2001). Such a congruency is important, since different types of reorganization can be found even in two distal hand muscles of the same patient (Balbi et al., 2000).

MEPs can be facilitated by voluntary pre-contraction of the target muscles. With this technique, ipsilateral responses could be elicited even in healthy adults (Wassermann et al., 1994; Ziemann et al., 1999). In order to obtain more highly discriminative results, we stimulated with the target muscles relaxed, since abnormal ipsilateral responses in congenital hemiparesis are also elicitable without pre-contraction (Maegaki et al., 1997). Continuous acoustic feedback of EMG activity in both forearms during the entire examination was given. Both hemispheres were searched for stimulation points eliciting contra- or ipsilateral MEPs. The optimal points (OP; defined as the scalp position where a reproducible muscle response was elicited with the lowest stimulation intensity) and their motor thresholds (MT; defined as the minimum stimulation intensity that produced at least five MEPs exceeding 50 μV in 10 trials) were determined separately. Latencies were measured from a superposition of three traces from consecutive stimulations over OP at 110% of MT. In each control subject, both hemispheres were assessed, but only one value for the MT and latency averaged from the results obtained during left and right hemisphere stimulation was used for statistical comparisons. This data reduction is necessary, since the results obtained during left and right hemisphere stimulation cannot be regarded as independent in individual subjects.

The absence of ipsilateral responses was documented by stimulation with 200% MT or 100% stimulator output (whatever was reached first) at the OP for the contralateral response, and at positions 1 cm and 2 cm anteriorly, posteriorly, laterally and medially. When no MEPs could be elicited by stimulation of the affected hemisphere, these stimulation positions were centred around a point analogous to the OP of the contralateral, unaffected hemisphere.

### Table 1 Demographic data and perinatal history in the 12 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at examination (years)</th>
<th>Side of hemiparesis</th>
<th>Prematurity/PCA (weeks)</th>
<th>Birth weight (g)</th>
<th>Pre-/perinatal complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>16</td>
<td>Left</td>
<td>–</td>
<td>3640</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>23</td>
<td>Right</td>
<td>–</td>
<td>3800</td>
<td>Cerclage at 33 weeks PCA</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>20</td>
<td>Right</td>
<td>–</td>
<td>3040</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>17</td>
<td>Right</td>
<td>–</td>
<td>3650</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>20</td>
<td>Left</td>
<td>–</td>
<td>3130</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>22</td>
<td>Right</td>
<td>33</td>
<td>2380</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>21</td>
<td>Right</td>
<td>–</td>
<td>3400</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>20</td>
<td>Right</td>
<td>–</td>
<td>3340</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
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<td>–</td>
<td>3070</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>18</td>
<td>Right</td>
<td>–</td>
<td>2300</td>
<td>Abnormal CTG, CS</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>19</td>
<td>Right</td>
<td>32</td>
<td>1300</td>
<td>Abnormal CTG, CS</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>25</td>
<td>Right</td>
<td>36</td>
<td>2500</td>
<td>–</td>
</tr>
</tbody>
</table>

CS = caesarean section; CTG = cardiotocogram.

Fig. 1 Individual structural and fMRI results (paretic hand movement) for all 12 patients. Left side: semi-coronal reconstructions (from T1-weighted 3D data sets) following anatomical landmarks of pyramidal tract somatotopy, illustrating the severity of structural damage to hand motor projections. A white figure-of-eight coil symbol indicates hemispheres from which MEPs in the paretic hand could be elicited (no TMS was performed in Patients 7, 11 and 12). Right side: individual fMRI activation patterns (SPM99, P < 0.05 corrected) during paretic hand movement. Since the activation in Patient 10 did not exceed this threshold, an uncorrected (P < 0.0001) threshold was used here, but only for illustration (*). The functional data are displayed on individual surface reconstructions calculated from normalized 3D data sets. Patients were sorted as in Tables 1 and 2 according to their MRI Lesion Index. Note that the images of the two patients with left-sided hemiparesis (1 and 5) were flipped, so that their affected (right) hemispheres also appear on the left side of this figure.
**Structural MRI**

All MRI measurements were performed on a conventional 1.5 Tesla Siemens Vision scanner (Siemens, Erlangen, Germany). Structural images were obtained as axial dual turbo spin-echo slices [TR (repetition time) = 4800 ms, TE (echo time) = 14 and 85 ms] and 3D data sets consisting of 128 contiguous sagittal T1-weighted slices [TR = 9.7 ms, TI (inversion time) = 300 ms, TE = 4 ms].
In each individual hemisphere, the ‘hand knob’ of the central sulcus was identified based on anatomical criteria (Yousry et al., 1997) and ‘primary sensorimotor cortex’ was defined as adjacent portions of the pre- and post-central gyri.

The method of assessment of the severity of structural damage to the hand motor projections of the pyramidal tract was as described previously (Staudt et al., 2000); this study included all but one patient from the current study. In brief, semi-coronal planes were reconstructed from the 3D data sets along two anatomical landmarks of pyramidal tract somatotopy. One landmark was the ‘hand knob’ of the precentral gyrus as the presumed cortical site from which hand motor projections originate. The second landmark was located in the anterior portion of the posterior limb of the internal capsule according to the somatotopic organization of fibres there. Thus, these image reconstructions approximately depicted the course of the hand motor projections in the central white matter. On these reconstructed planes, ventricular asymmetry was used as a measure of severity of the periventricular matter. On these reconstructed planes, ventricular asymmetry was used as a measure of severity of the periventricular lesions. These asymmetry ratios were included in the current study as the MRI Lesion Index. The asymmetry ratio of the one additional patient (U.E.), who did not take part in the previous study, was determined accordingly.

fMRI

Functional imaging data were acquired using a whole-brain multislice echo-planar imaging (EPI) sequence (Klose et al., 1999) (TE = 84 ms, 1 mm gap, 27 axial slices, voxel size $2 \times 2 \times 5$ mm) with an acquisition time of 4.87 s and an inter-scan interval of 8 s so that the scanning noise ceased for 3.13 s after each scan. The experiments were arranged in block designs, with alternations between four epochs of silent rest and four epochs of activation. Each epoch consisted of six scans, so that the total session comprised 48 scans. One such session was performed for each hand, i.e. the paretic and the non-paretic hand in the patients, and left and right hand in controls.

All subjects received detailed instructions before the measurement. They were asked to repetitively open and close the task hand with a frequency of ~1 Hz during the activation task; during the rest period, they were asked simply to lie still. The commands ‘now move’ and ‘now pause’ were given in the 3.13 s breaks between actual scanning at the beginning of the respective epochs. The examiner controlled task performance visually. The subjects had their eyes closed during the entire scanning procedure.

fMRI data analysis

Post-processing and statistical analysis of the functional images were performed using SPM99 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, University College, London, UK); default settings were used unless indicated otherwise. After realignment (including the adjustment for sampling errors), stereotactical normalization was performed using the averaged functional EPI image and the SPM EPI template, and the images were resliced to a resolution of $2 \times 2 \times 2$ mm voxels. Stereotactical normalization is a critical step in the analysis of data from patients with brain lesions as major distortions of anatomy can be caused by non-linear warping in the proximity of lesions (Brett et al., 2000). Therefore we used only data from the unaffected hemispheres for detailed topographical analyses. Subsequently, the data were smoothed with an anisotropic $6 \times 6 \times 15$ mm Gaussian kernel (thus tripling the original voxel size in each dimension) and high-pass filtered (cut-off period = 191 s). A boxcar function convolved with the modelled haemodynamic response function was used as basis function for the general linear model.

In a first step of statistical analysis, we calculated activation maps for each patient individually. An activation threshold of ($P < 0.05$) was applied at the voxel level corrected for multiple comparisons; this is equivalent to $T$ values of 5.78–6.00. An additional extent threshold of 5 voxels per cluster was introduced to enhance the clearness of the results by removing scattered small spots of activation. The total number of activated voxels, as well as the number of activated voxels in each cerebral hemisphere and in the interhemispheric fissure, were counted for each subject. Group comparisons of the activated volumes, expressed as the number of supra-threshold voxels, were performed with a Mann–Whitney U-test, using a $P < 0.05$ threshold for statistical significance, and accepting results of $P < 0.1$ as trends.

In the patients with activation of the unaffected, i.e. ipsilateral hemisphere during paretic hand movement, we assessed whether these activation sites were topographically different from the activations observed during movement of their non-paretic, contralateral hemisphere. This was done by calculating individual subtraction maps to search for areas in the unaffected hemispheres showing significantly more activation during paretic than during non-paretic hand movement.

Finally, voxel-wise statistical analyses were performed to obtain topographic information across groups of subjects. For these purposes, as for all illustrations, the patterns obtained from the two patients with left-sided hemiparesis were flipped, so that their affected right hemispheres also appeared on the left side of these maps. Similarly, we flipped all fMRI data obtained during left-hand movement in controls. Thus, we were able to calculate one average map combining both hands of each control for use in all voxel-wise comparisons with the patients. This procedure is necessary because left- and right-hand maps from one individual cannot be regarded as independent. Voxel-wise comparisons between groups of patients and between patients and controls were performed using a random-effect approach by calculating two-sample $t$-tests for the magnitude of signal change in each subject. This procedure is considered the only valid approach to compare
Table 2 Results of structural MRI, clinical assessment, TMS and fMRI in individual patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>MRI Lesion Index</th>
<th>Hand motor impairment</th>
<th>MM</th>
<th>Hemi (aff)</th>
<th>Hemi (unaff)</th>
<th>Paretic hand movement</th>
<th>Non-paretic hand movement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>paretic hand MEP</td>
<td>paretic hand MEP</td>
<td>non-paretic hand MEP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hemi (aff)</td>
<td>Hemi (unaff)</td>
<td>MFC</td>
<td>CBM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.82</td>
<td>1</td>
<td>–</td>
<td>17.0 ms; 43%</td>
<td>–</td>
<td>17.8 ms; 49%</td>
<td>547</td>
</tr>
<tr>
<td>2</td>
<td>0.90</td>
<td>1</td>
<td>–</td>
<td>20.3 ms; 43%</td>
<td>–</td>
<td>19.2 ms; 43%</td>
<td>1214</td>
</tr>
<tr>
<td>3</td>
<td>1.20</td>
<td>1</td>
<td>–</td>
<td>16.9 ms; 41%</td>
<td>–</td>
<td>15.4 ms; 33%</td>
<td>1880</td>
</tr>
<tr>
<td>4</td>
<td>1.32</td>
<td>1</td>
<td>–</td>
<td>17.3 ms; 39%</td>
<td>–</td>
<td>17.7 ms; 41%</td>
<td>1300</td>
</tr>
<tr>
<td>5</td>
<td>1.37</td>
<td>2</td>
<td>(+)</td>
<td>19.0 ms; 48%</td>
<td>16.4 ms; 36%</td>
<td>16.4 ms; 35%</td>
<td>208</td>
</tr>
<tr>
<td>6</td>
<td>1.51</td>
<td>2</td>
<td>n.d.</td>
<td>16.9 ms; 43%</td>
<td>18.8 ms; 57%</td>
<td>18.5 ms; 37%</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>1.61</td>
<td>2</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>577</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>1.63</td>
<td>2</td>
<td>n.d.</td>
<td>16.9 ms; 59%</td>
<td>16.4 ms; 57%</td>
<td>695</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>1.69</td>
<td>2</td>
<td>n.d.</td>
<td>17.2 ms; 45%</td>
<td>17.6 ms; 45%</td>
<td>1511</td>
<td>143</td>
</tr>
<tr>
<td>10</td>
<td>1.82</td>
<td>3</td>
<td>n.d.</td>
<td>17.1 ms; 32%</td>
<td>16.5 ms; 29%</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>11</td>
<td>2.14</td>
<td>3</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>1215</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>2.63</td>
<td>2</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>1394</td>
<td>179</td>
</tr>
</tbody>
</table>

All patients (mean ± SD)

Control data (mean ± SD)

Statistical significance

(+)Patient 6 did not show visible MM, but phasic EMG activity was present in forearm extensor muscles of the non-paretic hand during repetitive movement of the paretic hand.

* fMRI during paretic-hand movement did not yield any supra-threshold activation in Patient 10, probably due to task-related head movements. His fMRI data were therefore excluded from all group analyses. None of the control subjects showed ipsilateral MEPs, so the latencies and the MTs of ipsilateral MEPs in the patients were compared with the contralateral MEPs in controls. aff = affected; CBM = cerebellum; Hemi = hemisphere; MFC = mesial frontal cortex; n.d. = not determined; unaff = unaffected.
activation patterns between different samples of subjects (Friston et al., 1999). Because of the small sample sizes, these analyses have a rather low sensitivity. We therefore applied a less conservative threshold of $P < 0.005$ uncorrected, and corrected for multiple comparisons only at the cluster level ($P < 0.05$).

**Results**

**Clinical assessment and structural MRI**

Hand motor impairment was graded 1 in four patients, 2 in six patients, and 3 in two patients (Table 2). The MRI Lesion Indices for all patients are given in Table 2 and semi-coronal reconstructions along pyramidal tract somatotopy are displayed in Fig. 1. As shown previously (Staudt et al., 2000), there was a strong correlation between hand motor impairment and the MRI Lesion Index as a measure of periventricular damage to hand motor projections of the pyramidal tract ($r = 0.855$, $P < 0.001$, Spearman rank correlation, one-tailed; Fig. 2).

MM were observed during at least one of the assessed unimanual tasks in six out of 12 patients, and were always associated with a more severe impairment of the paretic hand (grades 2 and 3). Furthermore, MM were only present in patients with MRI Lesion Indices of $\geq 1.61$, whereas patients with indices of $\leq 1.51$ did not show MM, even when paretic hand function was similarly impaired (grade 2 in Patients 5 and 6; Fig. 2). Of all patients without visible MM, only Patient 6 showed subclinical, phasic EMG activity in forearm extensor muscles of the non-paretic hand during voluntary movements of the paretic hand.

**TMS data**

The TMS results (latencies, MT) for each patient, as well as the mean and SD of controls, are given in Table 2. Fig. 3 displays the MEP curves of Patients 1, 5 and 8.

TMS in controls ($n = 7$) elicited MEPs in the contralateral hand during left and right hemisphere stimulation, with latencies ranging from 15.5 ms to 19.3 ms (mean = 17.5 ms, SD = 1.2 ms) and MTs from 33% to 56% (mean = 43.8%, SD = 6.7%). None of the control subjects showed any MEPs in the ipsilateral hand.

TMS of the affected hemispheres in patients elicited MEPs in the contralateral (paretic) hand only in the six patients with MRI Lesion Indices of $\leq 1.51$, but not in the more severely affected patients with indices of $\geq 1.63$ (Fig. 2). Thus, the elicitability of contralateral MEPs by stimulation of the affected hemisphere was also associated with a better function of the paretic hand ($r = 0.738$, $P < 0.01$, Spearman rank correlation, one-tailed).

TMS of the unaffected hemispheres in patients elicited MEPs in the contralateral (non-paretic) hand in all subjects. Additional MEPs in the ipsilateral (paretic) hand were observed in all five patients with MRI Lesion Indices of $\geq 1.37$ (Fig. 2), and thus in all patients with more severely impaired paretic hands (grades 2 and 3). Compared with the MTs for the MEPs in the non-contralateral hand (29–57%), the MTs for the ipsilateral responses tended to be higher (range = 32–59%, mean difference = +5.2%, $P = 0.068$, Wilcoxon). No significant differences in latencies were observed; the ipsilateral projections conducted from 0.4 ms faster to 0.6 ms slower than the corresponding contralateral ones. The distances between the OPs for the ipsi- and contralateral responses were also minimal (<1 cm), without any systematic direction of deviation.

**Synopsis of clinical, structural MRI and TMS findings**

Two distinct groups of patients could be identified on the basis of these observations (see Fig. 3 for schematic illustration).

**Group SL (small lesions)**

The patients with excellent motor outcome (grade 1, $n = 4$) had the least severe structural damage to hand motor projections of the pyramidal tract (MRI Lesion Indices $\leq 1.32$). MEPs in the paretic hand could be elicited by TMS of the affected hemisphere, but not from the unaffected hemisphere.

**Group LL (large lesions)**

The patients with more severely impaired paretic hands (grades 2 and 3) and MM ($n = 6$) had the most severe structural damage to hand motor projections of the pyramidal tract.
tract (MRI Lesion Indices ≥1.61). No MEPs could be elicited by TMS of the affected hemisphere, but TMS of the unaffected hemisphere evoked MEPs in both the non-paretic and the paretic hand.

Patients 5 and 6, with intermediate-sized structural damage to hand motor projections (MRI Lesion Indices 1.37 and 1.51), combine characteristics from both groups. As was the case with the patients in group SL, these two patients did not show visible MM, although paretic hand function was as impaired as in most patients of group LL. Furthermore, MEPs in the paretic hand could be elicited by TMS of the affected hemisphere (as in group SL) and of the unaffected hemisphere (as in group LL).

**fMRI data**

For each experiment, the number of activated voxels on the convexity of each cerebral hemisphere, as well as in the mesial frontal region (activated voxels located on the mesial surfaces of the two frontal lobes) and the cerebellum, are given in Table 2.

fMRI of unimanual movement in controls showed strong activation in the respective contralateral central sensorimotor area both during right- and left-hand movement. Activation was also observed, in more variable degrees, in mesial frontal regions and in the ipsilateral cerebellum. In the ipsilateral cerebral hemisphere, however, activation never exceeded the conservative threshold used.

fMRI of paretic hand movement in patients (Fig. 1) showed activation of the contralateral, affected hemisphere in 11 out of 12 patients. In Patient 10, who showed severe task-related head movements during scanning, no supra-threshold activation was detected. This patient’s data were therefore excluded from all further analysis. In Fig. 1 (for the purpose of illustration only), his activation pattern is shown at a less conservative, uncorrected voxel threshold of $P < 0.0001$.

In contrast to all controls, the ipsilateral unaffected hemisphere also showed significant activation in eight cases (Table 2). The locations of these activated sites were quite variable, and included primary sensorimotor, premotor, prefrontal and parietal regions (Fig. 1).

fMRI of non-paretic hand movement in patients revealed activation of the contralateral, unaffected hemisphere in all 12 patients. Additional activation in the ipsilateral, affected hemisphere was observed in six patients (Table 2), which is again in contrast to all controls.

Topographical comparisons of activation during paretic and non-paretic hand movement were performed for all patients who showed activation in their unaffected hemisphere during movement of the ipsilateral, paretic hand ($n = 8$). In none of these subtraction analyses (activation during paretic hand movement minus activation during non-paretic hand movement) did we detect brain regions in the unaffected hemisphere that showed more activation during movement of the ipsilateral, paretic hand than during movement of the contralateral, non-paretic hand. In other words, areas in the unaffected hemisphere that were activated during paretic hand movements were also activated during movements of the non-paretic hand.
hand movement were also activated during movement of the non-paretic hand.

fMRI group comparisons (random-effect) of cortical activation evoked by movement of the paretic hand were performed for group SL ($n = 4$), group LL ($n = 6$) and the control group ($n = 6$). No group analysis was calculated for the two patients with intermediate-sized lesions. The results of all comparisons are summarized in Table 3.

In the unaffected hemisphere, group LL consistently showed stronger activation in the hand area of the primary sensorimotor cortex compared with both other groups (Fig. 4). Stronger activation in the unaffected hemisphere compared with controls was also observed in group SL (Fig. 4). This ipsilateral activation was, however, not located in the hand area of the primary sensorimotor cortex (as in group LL), but in a more anterior and inferior position, corresponding to premotor cortex (Brodman area 6). These two different sites of ipsilateral recruitment are compared in Fig. 5.

Since the paretic hand represents the patients’ non-dominant hand, and non-dominant hand movements have also been shown to yield stronger activation of the ipsilateral hemispheres in healthy subjects (Singh et al., 1998), we performed another set of random-effect comparisons, using only data obtained during left-hand movement in the controls. These comparisons of non-dominant hand movements confirmed stronger ipsilateral activation of primary sensorimotor

**Table 3** Random-effect comparisons of fMRI activation during paretic hand movement

<table>
<thead>
<tr>
<th></th>
<th>&gt; Group SL</th>
<th>&gt; Group LL</th>
<th>&gt; Controls</th>
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<tbody>
<tr>
<td>Group SL &gt;</td>
<td>CBM$_{\text{ipsi}}$ (16, –56, –26); $T = 11.73$</td>
<td>PMC$_{\text{unaff}}$ (40, –2, 34); $T = 10.22$</td>
<td>SMC$_{\text{eff}}$ (58, –28, 44); $T = 11.55$</td>
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<tr>
<td></td>
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<td>MFC (2, 14, 34); $T = 7.56$</td>
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<tr>
<td>Group LL &gt;</td>
<td>SMC$_{\text{unaff}}$ (40, –22, 58); $T = 9.21$</td>
<td>SMC$_{\text{unaff}}$ (42, –16, 60); $T = 7.57$</td>
<td>SMC$_{\text{eff}}$ (–44, –30, 52); $T = 9.18$</td>
</tr>
<tr>
<td></td>
<td>SPC$_{\text{unaff}}$ (38, –54, 54); $T = 8.79$</td>
<td>SPC$_{\text{unaff}}$ (38, –54, 54); $T = 8.79$</td>
<td>MFC (4, –10, 54); $T = 12.26$</td>
</tr>
<tr>
<td>Controls &gt;</td>
<td>No areas of significance</td>
<td>CBM$_{\text{ipsi}}$ (22, –56, –30); $T = 8.62$</td>
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Indicated are anatomical areas, stereotactical coordinates ($x$, $y$, $z$ in mm) using the Montreal Neurological Institute system and peak $T$-values. Only the results of the first two lines are depicted in Fig. 4. *aff* = affected hemisphere; CBM$_{\text{ipsi}}$ = cerebellum (ipsilateral to the paretic hand); MFC = mesial frontal cortex; PMC = premotor cortex; SMC = sensorimotor cortex; SPC = superior parietal cortex; unaff = unaffected hemisphere.

**Fig. 4** Random effect group comparisons of activation during paretic hand movement. For each comparison, areas showing significant differences in activation are superimposed on a sagittal (top) and axial (bottom) section of the SPM T1 single-subject template. The positions of these slices are determined by the global maximum of significance in the respective comparison. Not shown are the results for controls > group SL and controls > group LL (see Table 3). Hemi (aff) = affected hemisphere, Hemi (unaff) = unaffected hemisphere. SPM99, voxel threshold $P < 0.005$ uncorrected, extent threshold $P < 0.05$ corrected. The yellow arrow indicates the position of the central sulcus.
cortex in group LL (peak $T = 5.84$) and of premotor cortex in group SL ($T = 7.28$), where additional ipsilateral clusters were detected in prefrontal cortex (peak $T = 5.51$) and in the inferior parietal cortex (peak $T = 5.17$). Thus, the increased activation of the unaffected hemispheres in our patients can not, or not only, be attributed to the fact that paretic hand movements represent movements of their non-dominant hands.

In the affected hemisphere, both patient subgroups showed portions of the central sensorimotor region where brain activation was stronger than in controls (Fig. 4). This is in accordance with their overall larger activated volumes in the affected hemispheres (Table 2), but might also reflect differences in topography. Due to the uncertainties concerning stereotactical normalization in the proximity of brain lesions, we did not perform a more detailed topographical analysis for the affected hemisphere.

Also in accordance with the individual data, mesial frontal structures (supplementary and cingulate motor areas) showed significantly higher activation in both patient groups when compared with the control subjects (Fig. 4). Finally, as already suggested by the individual analyses of activated volumes (Table 2), subnormal cerebellar activation (ipsilateral to the paretic hand) was confirmed for group LL in the random-effect comparisons with the two other groups (Fig. 4 and Table 3).

**Discussion**

Patients with unilateral brain lesions are capable of a compensatory recruitment of brain structures in the unaffected hemisphere, especially when the lesions are acquired early in life. This has been demonstrated in a large number of studies, using different neurophysiological as well as functional imaging techniques. Here, we provide evidence for two different types of hand motor reorganization in the unaffected (ipsilateral) hemisphere, which could be separated on the basis of combined clinical, MRI, TMS and fMRI results: In the one group (SL), MEPs in the paretic hand were still elicitable by TMS of the affected (contralateral) hemisphere, indicating that the primary motor representation of the paretic hand had not changed. Nevertheless, fMRI demonstrated increased cortical activation in the unaffected hemisphere. Since no motor responses in the paretic hand could be elicited by TMS of these activated areas, they obviously act as non-primary motor areas. This pattern of ipsilateral reorganization was therefore termed the 'premotor type'.

In contrast, in the other group (LL), motor responses in the paretic hand were only elicitable by TMS of the unaffected (ipsilateral) hemisphere, so that, by definition, the primary motor representation of the paretic hand was located—abnormally—in the unaffected hemisphere of these patients. Accordingly, we termed this ipsilateral reorganization the 'primary motor type'.
These different TMS findings correlated with the severity of structural damage to hand motor projections of the pyramidal tract, as quantified on MRI reconstructions (Staudt et al., 2000). Intact crossed cortico-spinal projections were detected only up to MRI Lesion Indices of 1.51; abnormal ipsilateral projections arising from the unaffected hemisphere were detected in all patients with MRI Lesion Indices of $\geq 1.37$. The relevance of different lesion extents for the type of reorganization induced is further underlined by the two patients who combined neurophysiological criteria of both groups as their MRI Lesion Indices were indeed in-between these two critical thresholds (see Fig. 2).

**Ipsilateral reorganization of the premotor type**

This pattern was observed in patients with only minor lesions, in whom the cortico-spinal tract in the affected hemisphere was still able to exert sufficient motor control over the affected, contra-lesional hand. These patients showed only a very mild hand motor impairment, which is in accordance with previous descriptions of patients with preserved crossed cortico-spinal projections (group D in Carr et al., 1993; Maegaki et al., 1997; group C in Nezu et al., 1999). Based on neurophysiological data alone, brain organization in these patients seemed rather normal and, in particular, no evidence for reorganization in the unaffected hemisphere could be detected. fMRI during paretic hand movement, however, revealed a widespread activation in the unaffected, ipsilateral hemisphere in most of these patients, in addition to the expected activation of sensorimotor cortex in the affected hemisphere. Despite considerable inter-individual variability, the voxel-wise group analysis identified an area in the premotor cortex (Brodmann area 6), inferior and lateral to the central hand motor area, as a common denominator of increased ipsilateral activation. For this area, participation in ipsilateral hand movements has also been demonstrated in healthy subjects performing more complex finger movements (Catalan et al., 1998).

A similar constellation of TMS and functional imaging findings as in group SL has been reported for adult patients showing good recovery from hemiparetic stroke (for review, see Cramer and Bastings, 2000). In this population, excellent recovery of hand function also seems to depend on (at least partial) integrity of the crossed cortico-spinal tract, as indicated by the presence of MEPs in the paretic hand following TMS of the affected hemisphere (Binkofski et al., 1996; Turton et al., 1996; D’Olhaberrigaud et al., 1997; Byrnes et al., 1999). As in our patients, functional imaging in such well-recovered stroke patients revealed increased cortical activation in a network of mostly non-primary motor areas in the unaffected hemisphere (Chollet et al., 1991; Weiller et al., 1992, 1993; Cramer et al., 1997; Nelles et al., 1999), without any abnormal ipsilateral MEPs in the paretic hand when the unaffected hemisphere was stimulated by TMS (Binkofski et al., 1996). This type of ipsilateral activation has been attributed, at least in part, to the increased functional demand even simple hand movements pose on the sensorimotor network after structural damage to some of its components (Cramer and Bastings, 2000), since cortical activation patterns observed in healthy subjects when performing complex unimanual movements are very similar (Wexler et al., 1997; Catalan et al., 1998). Therefore, the patterns of ipsilateral recruitment we identified in group SL patients are apparently not specific for reorganization after brain lesions, and certainly not for lesions acquired early in life. It rather seems as if common mechanisms underlie this type of ipsilateral recruitment in response to increased functional demands during unimanual movements. This finding was somewhat unexpected, given the presumed greater reorganizational capability of the immature brain (Kennard, 1936).

**Ipsilateral reorganization of the primary motor type**

This pattern was observed in the more severely affected patients with lesions large enough to disrupt the cortico-spinal tract, as demonstrated by the absence of MEPs in the paretic hand when TMS was applied to the affected hemisphere. MEPs in the paretic hand could, however, be elicited by TMS of the unaffected hemisphere in all cases examined ($n = 3$), demonstrating the presence of abnormal, ipsilateral motor projections. Combined clinical, TMS and fMRI data could be obtained from two out of six patients of this group (Patients 8 and 9). In the other patients, either TMS data could not be acquired (pregnancy, Patient 12; no consent, Patients 7 and 11) or fMRI was hampered by motion artifacts (Patient 10), so that only two sets of data were available in these four subjects. Nevertheless, the available results in this group of patients were consistent and indicative of a common type of reorganization.

A large number of patients with this constellation of moderate hand motor impairment, marked MM and short-latency MEPs in the paretic hand by TMS of the unaffected hemisphere have been described in previous neurophysiological studies (Farmer et al., 1991; group A in Carr et al., 1993; Maegaki et al., 1997; group A in Nezu et al., 1999), and also in the reports that have combined fMRI and TMS (Nirkko et al., 1997; Macdonell et al., 1999; Thickbroom et al., 2001). In contrast to the reorganization of the premotor type, this mode of reorganization seems to be rather characteristic for early brain lesions (Carr et al., 1993; Maegaki et al., 1997; Nezu et al., 1999). To our knowledge, it has not been reported for lesions acquired beyond the age of 2 years (Maegaki et al., 1997). Age-dependency for the development of direct cortico-spinal pathways has also been established in experimental animal studies, where these pathways could no longer be induced by lesions inflicted after the animals had reached a critical age (Leong 1976; Kuang and Kalil, 1990). This phenomenon has been attributed to the presence of myelin-associated axonal growth inhibitors in more mature stages of brain development (Vanek et al., 1998).
It is important to differentiate the TMS phenomenon in this group of patients from ipsilateral MEPs that can be elicited in other conditions—as in patients with unilateral lesions acquired in adulthood (Benecke et al., 1991; Turton et al., 1996; Eyre et al., 2001) or later childhood (Nezu et al., 1999), in healthy children (Müller et al., 1997a; Eyre et al., 2001) or from pre-contracted forearm muscles in healthy adults (Wassermann et al., 1994; Ziemann et al., 1999). These ipsilateral MEPs usually have longer latencies, which has been interpreted as evidence for oligosynaptic, cortico-reticulo-spinal pathways (Benecke et al., 1991; Ziemann et al., 1999) or, alternatively, as indicating slower conduction velocities of such ipsilaterally projecting fibres (Eyre et al., 2001). As opposed to these, short-latency ipsilateral projections in distal muscles seem to be characteristic for congenital or early-onset hemiparesis. Similar observations have been reported only for rare genetically based anomalies such as congenital MM (Cohen et al., 1991), Klippel–Feil syndrome (Farmer et al., 1990) or Kallmann’s syndrome (Mayston et al., 1997).

In adult stroke patients, the detection of ipsilateral responses is believed to indicate poor recovery (Turton et al., 1996; Cramer and Bastings, 2000). This is probably because this phenomenon occurs as a consequence of demasking or disinhibition of ipsilateral pathways originating in the unaffected hemisphere, which is only caused by severe lesions disrupting not only descending cortico-spinal pathways, but also interhemispheric inhibitory connections. The situation is obviously different in congenital hemiparesis: although our study demonstrated that ipsilateral, fast-conducting projections were always associated with more severe impairment of hand function, all of these patients were able to grasp or even to perform some single-finger movements with their paretic hand. This is quite different from adult stroke patients, where the absence of MEPs in the paretic hand after TMS of the affected hemisphere is typically associated with a more or less complete loss of useful hand motor control (Pennisi et al., 1999). Accordingly, in the study by Carr and colleagues (Carr et al., 1993), the most severely affected patients were those with lesions acquired after 2 years of age and without MEPs in the paretic hand by neither stimulation of the affected nor of the unaffected hemisphere. This provides at least indirect evidence that reorganization of the cortico-spinal system with monosynaptic, fast-conducting projections arising in the unaffected hemisphere is advantageous for patients with extensive lesions to the cortico-spinal system, even if this compensation is incomplete and is accompanied by pronounced MM.

The strong activation of sensorimotor cortex in the affected hemispheres in group LL patients was unexpected. This means that, although no cortico-spinal pathways originated from this area any longer (as demonstrated by TMS), it still participated in the task-related changes of blood oxygenation detected by fMRI. Similar observations have been reported by Thickbroom and colleagues (Thickbroom et al., 2001), who attributed this activation of the affected hemisphere primarily to sensory feedback. This assumption of sensory stimulation from the paretic hand reaching the affected hemisphere would also be quite attractive in our patients. This would not only explain their activation of the affected hemisphere during paretic hand movement, but also during voluntary movement of the non-paretic hand, where the activation in the affected hemisphere could represent sensory feedback of MM in the paretic hand. A second hypothesis would be that these axotomized primary motor areas were transformed into areas of cortico-cortical processing, which are then embedded in a reorganized sensorimotor network. This would be supported by histopathological data demonstrating that axotomized pyramidal cells transform into interneurones (Marin-Padilla, 1997), so that additional cortico-cortical projections arise from these areas. Further support comes from studies in healthy subjects showing that the motor cortex of the precentral gyrus acts not only as a primary motor area (by sending motor volleys down the pyramidal tract), but can also play an important role in the planning, initiation and fine control of various motor tasks—especially in the ipsilateral hand (Chen et al., 1997)—without exerting direct motor control.

Also unexpected was the decrease in cerebellar activation in this subgroup of patients. This finding is, however, in line with recent PET data in patients with early lesions to the Rolandic cortex (Müller et al., 1997b). Because of the variability of hand motor performance in our patient sample, we cannot rule out that differences in the kinematics of the movement contributed to different amounts of cerebellar activation. Alternatively, the decrease in cerebellar activation could indicate disintegration of cerebro-cerebellar connectivity due to involvement of the fronto-ponto-cerebellar projections on their course through the periventricular white matter towards the anterior limb of the internal capsule in such patients with more extended lesions.

Patients with bilateral projections to the paretic hand

Motor responses in the paretic hand could be elicited by TMS of both hemispheres in Patients 5 and 6. This demonstrated (partial) integrity of the crossed cortico-spinal tract (as in group SL) and the presence of abnormal, ipsilateral projections (as in group LL). Thus, these two patients possess alternative pathways from both hemispheres to control the paretic hand. Similar TMS findings have been reported in only a few patients with congenital hemiparesis (Carr et al., 1993; Maegaki et al., 1997; Balbi et al., 2000; Thickbroom et al., 2001). In accordance with all these reported cases, this type of reorganization was not associated with visible MM in the non-paretic hand during paretic hand movements in our two patients. The absence of MM already suggested that motor control over the paretic hand should be (predominantly) exerted by the affected hemisphere via its intact, crossed cortico-spinal fibres. In the patient reported by Balbi...
and colleagues (Balbi et al., 2000), this assumption was confirmed by TMS producing a silent period in the voluntarily contracting affected hand only by stimulation of the affected hemisphere. Accordingly, fMRI during paretic hand movement showed activation only in the affected hemisphere in similar patients reported by Thickbroom and colleagues (Thickbroom et al., 2001) and in the two patients from our study.

This constellation allows further conclusions on the functionality of ipsilateral motor projections. In the patients who depend on such ipsilateral projections alone (group LL), hand motor function was always markedly impaired, suggesting that normal hand function cannot be achieved with this type of cortico-spinal reorganization. This hypothesis is further corroborated by the findings in patients with bilateral motor projections to the paretic hand: Although these patients differ from marked impairment of the paretic hand, they do not use the alternative pathways from the unaffected hemisphere they possess, but exert motor control over the paretic hand by the affected hemisphere. Apparently, their lesioned hemisphere with its partially intact crossed cortico-spinal tract is still better suited to control the paretic hand than the unaffected hemisphere despite its ipsilateral motor projections. This interpretation would, again, indicate a reduced functionality of reorganization with ipsilateral cortico-spinal projections. The question remains, however, what—if not activity—is responsible for the maintenance of these ipsilateral pathways?

**Anatomical substrates of ipsilateral motor projections in congenital hemiparesis**

Many studies on early-onset hemiparesis demonstrated the existence of abnormal, fast-conducting motor projections from the unaffected hemisphere to the paretic hand (e.g. Benecke et al., 1991; Farmer et al., 1991; Carr et al., 1993; Maegaki et al., 1997; Nezu et al., 1999). In the following, anatomical information on these pathways contributed by the results of this study, and by previous human and experimental animal investigations is summarized.

**Cortical origin of ipsilateral projections**

TMS studies providing topographical information on the scalp positions eliciting ipsilateral motor responses produced contradictory results. For many patients, the OPs for ipsi- and contra-lateral responses were described as identical (Maegaki et al., 1995, 1997; Watson and Colebatch, 1997; Thickbroom et al., 2001). This is in accordance with our TMS results. In contrast, some of the patients reported by Maegaki and colleagues (Maegaki et al., 1997) showed distances of 1–2 cm between the positions for ipsi- and contra-lateral responses. Pascual-Leone and colleagues (Pascual-Leone et al., 1992) even found two different sites from where ipsilateral responses could be elicited in hemispherectomy patients.

One site was in the area from where the normal contralateral responses could be evoked (with MEPs showing prolonged latencies) and the other 2–4 cm anterior to this position (with short-latency MEPs). A position of ~2 cm anterior to the position eliciting the normal contralateral response was also described by Kastrup and colleagues (Kastrup et al., 2000). These diverging results suggest that different sites might exist from where such ipsilateral projections originate. These may, again, depend on differences in timing, type, location and size of the lesions.

The detection of short-duration central peaks in EMG cross-correlograms of homologous hand muscles in such patients (Farmer et al., 1990, 1991; Carr et al., 1993) has been interpreted as evidence for common synaptic input into homologous motor neurone pools and, thus, to the existence of cortico-spinal axons originating in the primary motor cortex of the unaffected hemisphere that branch to reach alpha-motoneurones on both sides of the spinal cord. This hypothesis would imply that the ipsilateral projections to the paretic hand originate not only from the same area as the normal, crossed pyramidal tract, but that they actually arise from the very same cortical pyramidal neurones (Fig. 6A). Alternatively, such central peaks could also indicate intra-cortical synchronization of contra- and ipsilaterally projecting cortico-spinal neurones arising from similar areas of the intact hemisphere (Farmer et al., 1990; Conway et al., 1995; Eyre et al., 2001).

As opposed to these more indirect data, fMRI can directly visualize which cortical areas are active during paretic hand movement, although the interpretation is somewhat hampered in the presence of marked MM. In our experiments, activation in the unaffected hemisphere during paretic hand movement was located in the hand area of the sensorimotor cortex. This is in accordance with other studies combining TMS and fMRI (Nirrko et al., 1997; Macdonell et al., 1999; Thickbroom et al., 2001). In the study by Macdonell and colleagues, activation during paretic hand movement was observed "in the same area and slightly more inferiorly in the precentral gyrus" than the activation produced by contralateral, non-paretic hand movement. On visual comparison, such minor differences were also evident in our patients; however, when topographical differences between the patterns for paretic and non-paretic hand movement were tested directly by a subtraction analysis, we did not detect any region in the unaffected hemisphere that was more active during paretic than during non-paretic hand movement. This argues against the existence of brain structures in the unaffected hemisphere subserving paretic hand function exclusively, at least in the patients in this study.

**Course of ipsilateral projections in the spinal cord**

This topic has also been a matter of some debate (see Fig. 6 for schematic illustration of possibilities). Nirrko and...
Mechanisms for the development of ipsilateral projections

Two different mechanisms have been suggested. First, local factors signalling denervation of spinal neurones on the paretic side could induce axonal sprouting in normal crossed cortico-spinal axons originating in the unaffected hemisphere and projecting contralaterally. These new collaterals would then re-cross the midline to innervate motor neurones on the paretic side (Fig. 6A). Such collateral branching with single cortico-spinal neurones projecting to both sides of the spinal cord was indeed observed histologically in animal studies (Kuang and Kalil, 1990). In patients with congenital hemiparesis, the existence of such branched cortico-spinal axons has been inferred from the detection of short-duration central peaks in EMG cross-correlation analyses as indicators of common synaptic input into homologous motor neurone pools (Farmer et al., 1991; Carr et al., 1993).

Secondly, normally transient ipsilateral projections could be preserved from previous stages of development, with the lesion preventing the ‘pruning’ of these connections in a phase of activity-dependent cortico-spinal tract remodelling (Martin et al., 1999). Accordingly, in human subjects with early-onset hemiparesis, the existence of unbranched, ipsilaterally projecting fibres (Fig. 6B) has also been suggested by neurophysiological data (group B in Carr et al., 1993; Eyre et al., 2001) and in histopathological investigations describing an increased number of axons in the pyramid of the unaffected side of such patients (Scales and Collins, 1972). Cincotta and colleagues (Cincotta et al., 2000) even demonstrated the co-existence of branched and unbranched fibres in a patient with congenital hemiparesis—so both mechanisms might be relevant. This has also been suggested from experimental animal data (Martin et al., 1999).

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