Cortical activation by tactile and painful stimuli in hemispherectomized patients

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Summary
Hemispherectomized patients are able to perceive tactile and painful stimuli on their nonparetic as well as paretic body halves. We have used functional MRI to study the cortical mechanisms underlying this preserved somatosensory capacity. Nonpainful brushing and painful heat were applied to the skin of the legs in four hemispherectomized patients and, for comparison, in four normal subjects. Cortical activation was studied with a 1.5 T scanner using a BOLD (blood oxygen level dependent) protocol. All patients rated both the brushing and the heat pain as almost equally intense on each leg and the ratings were similar to those in normals. Brushing on the nonparetic leg activated primary and secondary somatosensory cortices (S1 and S2) in all patients, similar to findings in normals. Brushing on the paretic leg activated S1 in two patients and S2 in one of these patients. Heat pain activated S2, insular cortex and anterior cingulate cortex to a similar degree for both legs, but the activation was weaker in the patients than in the normals. For the individual patient, there was generally no obvious correlation between cortical activation as studied with the BOLD technique and psychophysical performance. The findings from tactile stimulation of the nonparetic leg, that the activation was similar to the contralateral activation in normals, suggest that tactile information processing in the hemisphere contralateral to the stimulation is independent of the corpus callosum. In contrast, the pain activation for the nonparetic leg was weaker than in normals, suggesting that pain activation in the hemisphere contralateral to the stimulation is dependent on transcallosal information processing. The latter finding was corroborated by a subnormal capacity for pain localization on the nonparetic foot in two of the patients. The findings from stimulation of the paretic leg show that areas typically involved in the processing of tactile and painful stimuli can be activated by ipsilateral pathways directly from the periphery. The tactile-evoked ipsilateral S1 activation may be due to subcortical reorganization, since it was not observed in the normal subjects.

Keywords: hemispherectomy; touch; pain; functional MRI; cortex

Abbreviations: fMRI = functional magnetic resonance imaging; BOLD = blood oxygen level dependent; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; IC = insular cortex; ACC = anterior cingulate cortex; MEG = magnetoencephalography; FWHM = full-width-half-maximum

Introduction
Somatosensation is generally considered to be served by brain structures contralateral to the stimulation. Consequently, lesions of the primary and secondary somatosensory cortices (S1 and S2) typically cause severe contralateral disturbances in tactile and pain sensibility (Corkin et al., 1970; Norrell, 1980; Greenspan et al., 1999). Nevertheless, for a long time it has been known that somatosensation may also be served by ipsilateral brain structures. This is unequivocally demonstrated in patients with total unilateral cerebral hemispherectomies, who sometimes show a remarkable preservation of tactile and pain sensibility (Dandy, 1933; Muller et al., 1991). There is also other evidence of ipsilateral information processing in man. Noordenbos and Wall described a patient with spinal cord transection, with saving of only part of one anterolateral quadrant, who could perceive tactile and painful stimuli on both body halves (Noordenbos and Wall, 1976). Sperry and others have shown that patients with corpus callosum transection can report tactile and painful
stimuli from either body half (Sperry et al., 1969; Norrsell, 1973; Stein et al., 1989).

Cortical activation and tactile stimulation

Brain imaging studies in healthy subjects typically show a tactile-related activation in contralateral S1 and bilateral S2 (Fox et al., 1987; Coghill et al., 1994; Polonara et al., 1999). The ipsilateral S2 activation could, in theory, be mediated directly from the thalamus or via the corpus callosum (Simoes and Hari, 1999). The idea of an ipsilateral activation directly from the thalamus was supported by a recent magnetoencephalography (MEG) recording of ipsilateral S2 activation in a patient whose contralateral S1 and S2 were destroyed by a stroke (Forss et al., 1999). However, in a MEG study on normal subjects, S2 on the side ipsilateral to the stimulus was activated 10–20 ms after the activation of the contralateral S2, suggesting that the ipsilateral activation comes mainly from the contralateral hemisphere (Karhu and Tesche, 1999). Ipsilateral S1 is typically not activated in brain imaging studies on normals (Disbrow et al., 1998). However, it cannot be excluded that this is a methodological problem since there are reports of ipsilateral S1 activation following stimulation of the hand (Schnitzler et al., 1995; Hansson and Brismar, 1999). In monkeys it was shown that ipsilateral S1 could only be activated if the contralateral S1 was intact and it was concluded that the ipsilateral S1 activation is most likely to be mediated via transcallosal pathways (Iwamura et al., 1994).

There are two previous functional MRI (fMRI) studies of tactile stimulation in hemispherectomized patients (Graveline et al., 1998; Bittar et al., 2000). Graveline and colleagues reported a significant ipsilateral activation posterior to S1 in what they called associative somatosensory areas, but did not report any ipsilateral activation in S1 or S2. Bittar and co-workers observed ipsilateral S2 activation in all three of their patients but no activation in ipsilateral S1.

Cortical activation and painful stimulation

In brain imaging studies on healthy subjects, the cortical regions most commonly activated by a painful stimulus include contralateral S1 and bilateral S2, insular cortex (IC) and anterior cingulate cortex (ACC) (for reviews, see Ingvar, 1999; Bushnell et al., 2000). However, it is not known to what extent the ipsilateral activations are mediated directly from the periphery or via the corpus callosum (Coghill et al., 1999). In monkeys a substantial proportion of nociceptive neurones in the medial and posterior thalamus have bilateral receptive fields, and there is anatomical evidence of independent projections from the thalamus to S2, IC and ACC (for a review, see Apkarian, 1995). This suggests that the ipsilateral activation observed in human brain imaging studies may not necessarily be mediated via the corpus callosum. In a brain imaging study of central pain following right-sided parietal stroke, pain-related activation was observed in the left S2/IC following allodynic stimulation of the left thigh (Peyron et al., 2000). However, the patient also had activation in a remainder of the right S2/IC area and it cannot be excluded that the ipsilateral activation was mediated via transcallosal pathways.

About half of studies imaging pain in humans show activation of S1 (Bushnell et al., 1999). This variability may have several explanations including cognitive factors such as attention and previous pain experience and also procedural and analytical differences among the studies (Bushnell et al., 1999). The pain-related S1 activation, when reported, is evoked from the contralateral body half; and in monkeys thalamic nociceptive neurones that likely project to S1 have strictly contralateral receptive fields (Kenshalo et al., 1980; Bushnell, 1995). In the monkey, although the majority of nociceptive neurones in S1 have contralateral receptive fields (Tommerdahl et al., 1998; Kenshalo et al., 2000), there are also some nociceptive S1 neurones with large bilateral receptive fields (Kenshalo and Isenesee, 1983). However, as for tactile stimulation, the S1 response to ipsilateral stimulation could be mediated via transcallosal pathways.

We have used fMRI to study cortical activation evoked by tactile and painful stimuli in hemispherectomized patients and in normals. Tactile stimulation of the nonparetic leg regularly activated S1 and S2, similar to the activation observed in the hemisphere contralateral to the stimulus in normals. On the other hand, painful stimulation of the nonparetic leg evoked a weaker cortical activation than in normals. Tactile and painful stimulation of the paretic leg activated similar areas as stimulation of the nonparetic leg, showing that these areas (S1, S2, IC and ACC) can be activated by ipsilateral pathways directly from the periphery. Preliminary reports have been published (Marchand et al., 1999; Morin et al. 1999).

Material and methods

Patients and normal subjects

Four patients (aged 25–46 years) participated in the study. They developed hemiparesis in early childhood and had undergone functional or anatomical cerebral hemispherectomy for the relief of intractable epileptic seizures. The patients’ case histories, including surgical procedures, have been reported previously in detail (Tomaiuolo et al., 1997). In addition, eight neurologically intact subjects (aged 22–51 years) were studied. They were staff or students at the Department of Physiology, McGill University. Informed consent was obtained from all subjects, the study was performed according to the Declaration of Helsinki and the Ethics and Research Committee of the Montreal Neurological Institute and Hospital approved the procedure.

Imaging and stimulation procedures

MRI was performed using a 1.5 T Siemens Vision scanner (Siemens Medical Systems, Evingen, Germany) with a
standard head-coil. For the patients (n = 4) each session consisted of one anatomical and six functional scannings: three functional scannings for stimulation of each leg. For the normals (n = 4) each session consisted of one anatomical and two to four functional scannings and the stimulus was always applied to the left leg. The anatomical scans were collected using a high-resolution T1-weighted anatomical protocol [TR (repetition time), 22 ms; TE (echo time), 20 ms; flip angle 30°; FOV (field of view), 256 mm]. The functional scans were collected using a blood oxygen level dependent (BOLD) protocol with a T2*-weighted gradient echo echo-planar imaging sequence (TR 3.4 s; TE 51 ms; flip angle 90°). Each functional scan consisted of 120 volume acquisitions (13 slices, 7 mm thickness, 2.3 × 2.3 mm in-plane resolution). The scanning planes were oriented parallel to the anterior commissure–posterior commissure line and covered from the top of the cortex down to the base of the thalamus.

At least two scanning sessions were made during which either a tactile or thermal stimulus was manually applied to the skin on the medial side of the leg, 15 cm inferior to the patella. The participants were instructed to attend to the stimulus, to keep their eyes closed and not to move. Tactile stimuli were applied as repetitive strokings with a 7-cm-wide soft artist’s brush (speed 20 cm/s, distance 10 cm). Thermal stimuli were applied using two 9 cm² contact thermodes heated by circulating water. Prior to the scanning, a series of different thermode temperatures was presented to the participants and one temperature that was rated as moderately painful (44–47°C) and one that was rated as slightly warm (34–36°C) were chosen for the scanning session. There were no consistent differences between the temperatures chosen for the patients and for the normals.

A tactile stimulation scan consisted of 20 cycles of three volume acquisitions with no stimulation followed by three volume acquisitions with brushing (Fig. 1A). A thermal stimulation scan consisted of 10 cycles of three volume acquisitions with no stimulation followed by three volume acquisitions with painful heat, three volume acquisitions with no stimulation and, lastly, three volume acquisitions with nonpainful warm (Fig. 1B). One volume acquisition lasted 3.4 s yielding a scanning time of 6.8 min.

After each scan, the participants were asked to rate their remembrance of the intensity of the stimulus at the beginning of the scan, at the end of the scan and when it was most intense. For brushing, which was never painful, zero represented no sensation and five represented a very intense sensation. For noxious thermal stimulation, the patients were asked to rate pain intensity and unpleasantness on separate scales (Rainville et al. 1992). For the intensity scale, zero represented no pain sensation and five the most intense pain sensation imaginable. For the unpleasantness scale, zero represented not at all unpleasant and five the most unpleasant pain imaginable. Unpleasantness ratings were not obtained for the normals. In order to minimize head movements, all ratings were given non-verbally, using the fingers of one hand.

**Image processing and analyses**

Data processing was carried out with software developed at the Montreal Neurological Institute, Montreal, Canada. Functional data were motion corrected by registering all volume acquisitions to the third volume in the scan, low-pass filtered with a 6 mm full-width-half-maximum (FWHM) Gaussian kernel in order to increase the signal to noise ratio; the first two volumes were excluded to assure steady-state condition. All images were resampled into stereotaxic space (Collins et al., 1994).

The statistical analysis of the fMRI data was based on a linear model with correlated errors. For each scan, the design matrix of the linear model was first convolved with a gamma haemodynamic response function with a mean lag of 6 s and a standard deviation of 3 s timed to coincide with the acquisition of each slice (Lange and Zeger, 1997). Drift was removed by adding polynomial covariates in the frame times, up to 3 degrees, to the design matrix. The correlation structure was modelled as an autoregressive process of 1 degree. At each voxel, the autocorrelation parameter was estimated from the least square residuals using the Yule–Walker equations, after a bias correction for correlations induced by the linear model. The autocorrelation parameter was first regularized by spatial smoothing with a 15 mm FWHM Gaussian filter, then used to ‘whiten’ the data and the design matrix. The linear model was then re-estimated using least squares on the ‘whitened’ data to produce estimates of effects and their standard errors.
The resulting t-statistic images were thresholded (P = 0.05) using the minimum given by a Bonferroni correction and random field theory (Worsley et al., 1996). For tactile stimulation the t-statistic image reflected the difference in activation between the brushing and no stimulation conditions, whereas for thermal stimulation it reflected the difference in activation between the painful hot and nonpainful warm conditions.

The analyses were generally made on the average of three individual scans for each leg. One exception was thermal stimulation for the patient S.E., where the analyses were made on the average of six individual scans, collected on separate days. The reason for six scans in S.E. was that we did not find any significant activation for the nonparetic leg in the first session and we wanted to ensure that this was not due to technical problems. Directed searches were performed in S1 and S2 for tactile stimulation and in S1, S2, IC and ACC for thermal stimulation. These were the only cortical areas that were significantly activated, across a group of normal subjects, by similar tactile and painful stimuli in a related fMRI study on normals (Ha et al., 1998). Based on this study (Ha et al., 1998), the search volume for S2 was estimated to be 10.1 cm³ (1260 voxels), for IC to 6.2 cm³ (780 voxels) and for ACC to 9.6 cm³ (1200 voxels). The S1 search volume was defined by the anatomy of the postcentral gyrus and was estimated to be 12.1 cm³ (1508 voxels). For a directed search within these volumes the t-values for significant activation were calculated to 3.6 for S1, S2 and ACC, and 3.5 for IC.

The volume of one hemisphere was estimated to be 600 cm³ (75 000 voxels) yielding a threshold t-value of 4.6 for a global search in the hemispherectomized patients and a threshold t-value of 4.8 for a global search in the normals. Data were not analysed for negative stimulus correlations.

Psychophysical testing of the ability to localize tactile and painful stimuli

The patients’ ability to determine whether a stimulus was applied to the nonparetic or paretic leg was tested experimentally. For tactile localization the patients (n = 4) were touched with a monofilament (bending force 110 mN) that was never perceived as painful and asked which leg was stimulated. For pain localization, two identical thermodes were placed on the skin using the same painful and nonpainful thermode temperatures as during the scanning. The nonpainful and painful temperatures were the same as during the scanning. The normal subjects who had not been scanned (n = 4) the warm and hot temperatures were chosen prior to the testing in the same way as was done before the scanning for the other participants (cf. above).

All localization tests were carried out with the participants’ eyes closed and all responses were given verbally.

The stimulation procedure was repeated 20 times for each foot, with equal numbers of painful stimuli applied to the first and the fifth toes, in a pseudorandom order. This test was also applied to one of the feet of the normal subjects (n = 7). The nonpainful and painful temperatures were the same as during the scanning. For the normal subjects who had not been scanned (n = 4) the warm and hot temperatures were chosen prior to the testing in the same way as was done before the scanning for the other participants (cf. above).

Results

Tactile stimulation

The patients rated the brushing as equally intense for the two legs (t-test, P = 0.97; Fig. 2) and there was no significant difference (t-test, P = 0.10) in intensity ratings between patients (mean = 2.5) and normals (mean = 2.0). Even though the patients rated the brushing as equally intense for both legs, the t-values within S1 and S2 were significantly higher (Wilcoxon, P < 0.05) for stimulation of the nonparetic (median 6.0) than the paretic (median < 3) leg (Tables 1 and 2). Within contralateral S1 and S2, there was no significant difference (Wilcoxon, P = 0.57) between the t-values evoked by brushing of the nonparetic leg (median 6.0) and the t-values evoked by brushing of the left leg in normals (median 5.6) (Tables 1 and 3).

S1 activation

Brushing the nonparetic leg in all patients and brushing the left leg in all but one of the normals produced a significant S1 activation (Tables 1 and 3). From the stereotaxic coordinates it may be noted that the activations were located posterior to what is indicated as S1 in the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). Nevertheless, the activations were clearly in the postcentral gyrus (Sobel et al., 1993).
For the paretic leg a significant S1 activation was only seen for J.B. and I.G., whereas for S.E. and D.R. the stimulus-related activity within the ipsilateral S1 search volume was far from significant (Table 2). An example of the time-course of the BOLD signal in S1 for brushing on the paretic leg is shown in Fig. 1A, demonstrating the normal lag between onset of the brushing and peak of the BOLD signal.

For J.B. the peaks of the S1 t-values for stimulation on the nonparetic and paretic legs were separated by 17 mm (Fig. 3 and Tables 1 and 2). The volume of the S1 activation for the nonparetic leg was larger (2.5 cm³, 307 voxels) than for the paretic leg (1.7 cm³, 210 voxels). The volumes overlapped partially and for the nonparetic leg the activation was also significant at the location of the peak t-value for the paretic side. The reverse was not true; the spot of the peak t-value for the nonparetic leg was not significantly activated for the paretic leg.

For I.G. the peaks of the S1 t-values for stimulation on the nonparetic and paretic legs were separated by 4 mm (Fig. 3 and Tables 1 and 2). For the nonparetic leg the activated volume was 0.3 cm³ (37 voxels), whereas for the paretic leg it was 0.05 cm³ (6 voxels). As in J.B., the S1 activation for the nonparetic leg was also significant at the location of the peak t-value for the paretic side, but the reverse was not true.

**S2 activation**

Brushing the nonparetic leg in all patients and brushing the left leg in all normals showed a significant S2 activation (Tables 1 and 3). Generally, the S2 activation focus was located medially on the superior bank of the lateral sulcus. This is consistent with other data showing a somatotopic organization of S2 with the foot located medially to the hand (Ruben et al., 2000). For the paretic leg, only J.B. showed a significant S2 activation (Table 2) and the peaks of the t-values for stimulation on the nonparetic and paretic legs were separated by only 2 mm with overlapping volumes (Fig. 3 and Tables 1 and 2). However, the volume of the activation was larger for the nonparetic (3.4 cm³, 419 voxels) than for the paretic side (2.1 cm³, 265 voxels). For the other patients the stimulus-related activity within the ipsilateral S2 area was far from significant (Table 2).

### Table 1 Brushing of the nonparetic leg

<table>
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<th>S.E.</th>
<th>D.R.</th>
<th>J.B.</th>
<th>I.G.</th>
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<tbody>
<tr>
<td>S1</td>
<td>6.1 (–22, –38, 74)</td>
<td>5.2 (–18, –46, 74)</td>
<td>10.2 (12, –44, 72)</td>
<td>6.0 (–18, –48, 52)</td>
</tr>
<tr>
<td>S2</td>
<td>5.3 (–48, –38, 16)</td>
<td>6.4 (–58, –24, 20)</td>
<td>9.6 (46, –30, 28)</td>
<td>3.7 (–42, –34, 14)</td>
</tr>
<tr>
<td>Other activated areas</td>
<td>5.5 (–18, –52, 68; BA 5)</td>
<td>5.0 (–52, 4, 28; BA 6)</td>
<td>4.8 (42, –72, 2; BA 19)</td>
<td>4.8 (26, –36, 46; BA 40)</td>
</tr>
</tbody>
</table>

Peak t-values and stereotaxic coordinates (within parentheses) are shown for different patients and brain regions. t-Values ≥3.6 within S1 and S2, and t-values ≥4.6 in other areas represent significant activity (P < 0.05) and are shown in bold. The coordinates are expressed in millimetres and refer to the medial–lateral (relative to midline, positive = right), anterior–posterior (relative to anterior commissure, positive = anterior) and superior–inferior (relative to commissural line, positive = superior) stereotaxic planes (Talairach and Tournoux, 1988; Coghill et al., 1994). BA = Brodmann area.

### Table 2 Brushing of the paretic leg

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<tr>
<td>S1</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>10.3 (16, –46, 56)</td>
<td>4.5 (–14, –50, 52)</td>
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<tr>
<td>S2</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>8.3 (46, –32, 28)</td>
<td>&lt;3</td>
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<tr>
<td>Other activated areas</td>
<td>–</td>
<td>–</td>
<td>5.8 (36, –6, 66; BA 6)</td>
<td>–</td>
</tr>
</tbody>
</table>

Peak t-values and stereotaxic coordinates (within parentheses, see Table 1 for explanation) are shown for different patients and brain regions. t-Values in bold indicate significant activity (P < 0.05).

BA = Brodmann area.

For patients as well as normals the highest significant t-values were always found in either S1 or S2. However, in a global search (see Methods) significant activity was found also in other areas (Tables 1–3). Similar to several other studies, we failed to observe significant activity in the thalamus (Fox et al., 1987; Coghill et al., 1994; Disbrow et al., 1998).

**Other activated areas**

For all noxious heat stimuli were clearly painful and there were no consistent side differences in the patients’ ratings of pain intensity (t-test, P = 0.77; Fig. 4A). Neither was there any significant difference (t-test, P = 0.20) in pain intensity ratings between patients (mean = 3.3) and normals (mean = 4.0). Furthermore, there were no consistent side differences in the patients’ ratings of the unpleasantness of the stimulation (t-test, P = 0.58; Fig. 4B). Nevertheless, I.G. rated the unpleasantness more than twice as high on the paretic than the nonparetic leg. Ratings of unpleasantness were not
Fig. 3 Cortical activation evoked by brushing of the nonparetic and paretic legs. The right side of the images corresponds to the right side of the patient and red circles indicate regions of interest. t-Values $\geq 3.6$ within the S1 and S2 search volumes (see Methods) represent significant activity ($P < 0.05$), and t-values $> 6$ are indicated by white colour. The stereotaxic coordinates of the activations are indicated in Tables 1 and 2.
obtained for the normals, but studies in our laboratory using similar thermal stimuli show a high correlation between intensity and unpleasantness ratings of experimental heat pain (Rainville et al., 1992, 1997).

**S1, S2, IC and ACC activation**

Even though the patients gave similar pain intensity ratings as the normals, the pain-evoked activation was poor compared to that of the normals (Tables 4–6). Within S1, S2, IC and ACC contralateral to the stimulation, significantly lower t-values (Wilcoxon, \( P < 0.001 \)) were obtained in the patients (median <3.0) compared with the normals (median = 6.0).

None of the patients showed activation in S1, whereas contralateral S1 was activated in all but one of the normals (Tables 4–6). In the patients, the areas that could be activated by a contralateral stimulus (S2, IC and ACC) could also be activated by an ipsilateral stimulus directly from the periphery (Fig. 5). In contrast to tactile stimulation, there was no significant side difference (Wilcoxon, \( P = 0.46 \)) in the t-values within S2, IC and ACC for stimulation of the nonparetic (median = 3.6) and paretic (median <3.0) legs.

The distance between the peaks of the two S2 activations in I.G. was 8 mm and the activation was larger for the nonparetic (0.8 cm\(^3\), 97 voxels) than the paretic leg (0.5 cm\(^3\), 64 voxels). The volumes overlapped partially and for the nonparetic leg, the activation was also significant at the location of the peak t-value for the paretic side. The reverse was not true; the spot of the peak t-value for the nonparetic leg was not significantly activated for the paretic leg. The distance between the peaks of the two IC activations in D.R. was 14 mm and the activation was about 20 times larger for the nonparetic (1.2 cm\(^3\), 148 voxels) than the paretic leg (0.06 cm\(^3\), 7 voxels). For the nonparetic leg, the activation at the location of the peak t-value for the paretic side approached significance (\( t = 3.1 \)), whereas the spot of the peak t-value for the nonparetic leg was far from being significantly activated for the paretic leg. The distance between the peak of the two ACC activations in I.G. was only 2 mm with overlapping volumes. The activation was smaller for the nonparetic (0.5 cm\(^3\), 60 voxels) than the paretic leg (1.2 cm\(^3\), 153 voxels).

**Other activated areas**

In a global search, significant activity was found in several other areas besides S1, S2, IC and ACC, notably for the normals (Tables 4–6). Similar to tactile stimulation and other studies (Davis et al., 1998; Disbrow et al., 1998; Ha et al., 1998), we did not, except for one subject, S.J. (see Table 6), observe significant pain-related activity in the thalamus.

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**Table 3 Brushing of the left leg in normals**

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<tr>
<th></th>
<th>H.B.</th>
<th>C.J.</th>
<th>B.J.</th>
<th>S.J.*</th>
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<tbody>
<tr>
<td>S1 (contra)</td>
<td>3.2 (10, –42, 70)</td>
<td>7.4 (20, –38, 76)</td>
<td>5.2 (12, –30, 80)</td>
<td>5.3 (22, –36, 56)</td>
</tr>
<tr>
<td>S2 (contra)</td>
<td>5.9 (54, –26, 18)</td>
<td>9.1 (50, –38, 26)</td>
<td>4.7 (42, –24, 14)</td>
<td>9.7 (50, –22, 14)</td>
</tr>
<tr>
<td>S2 (ipsi)</td>
<td>6.3 (–48, –38, 24)</td>
<td>6.0 (–54, –36, 30)</td>
<td>5.1 (–50, –24, 18)</td>
<td>8.0 (–60, –18, 22)</td>
</tr>
<tr>
<td>Other activated cortical areas</td>
<td>5.8 (–48, –74, 8; BA 19)</td>
<td>7.2 (56, –58, 12; BA 37)</td>
<td>–</td>
<td>5.3 (42, –36, 62; BA 7)</td>
</tr>
<tr>
<td></td>
<td>5.6 (–54, –30, 52; BA 40)</td>
<td>6.2 (52, 6, 34; BA 6)</td>
<td>–</td>
<td>5.1 (52, –2, 4; BA 22)</td>
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<tr>
<td></td>
<td>5.1 (–48, –58, 4; BA 37)</td>
<td>5.9 (–54, –18, 36; BA 4)</td>
<td>–</td>
<td>5.1 (32, –6, 52; BA 4)</td>
</tr>
<tr>
<td></td>
<td>4.9 (–54, –4, 48; BA 4)</td>
<td>5.4 (–2, 4, 62; BA 6)</td>
<td>–</td>
<td>5.1 (34, 66, –2; BA 10)</td>
</tr>
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Peak t-values and stereotaxic coordinates (within parentheses, see Table 1 for explanation) are shown for different normal subjects and brain regions. \( t \)-Values \( \geq 3.6 \) within the S1 and S2 areas and \( t \)-values \( \geq 4.8 \) in other areas represent significant activity (\( P < 0.05 \)) and are shown in bold. BA = Brodmann area. *Data from two scannings.
Other activated areas

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<td>S1</td>
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<tr>
<td>S2</td>
<td>&lt;3</td>
<td><strong>4.1</strong> (–38, –20, 20)</td>
<td>3.5 (44, 28, 30)</td>
<td><strong>4.5</strong> (–64, –32, 16)</td>
</tr>
<tr>
<td>IC</td>
<td>&lt;3</td>
<td><strong>4.4</strong> (–38, 16, 4)</td>
<td><strong>3.6</strong> (40, 4, –4)</td>
<td><strong>3.6</strong> (–44, 2, 8)</td>
</tr>
<tr>
<td>ACC</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td><strong>5.2</strong> (–6, –8, 48)</td>
</tr>
<tr>
<td>Other activated areas</td>
<td>–</td>
<td><strong>4.6</strong> (–50, –16, 20; BA 43)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Peak t-values and stereotaxic coordinates (within parentheses, see Table 1 for explanation) are shown for different patients and brain regions. t-Values ≥3.6 within S1, S2 and ACC, t-values ≥3.5 within IC, and t-values ≥4.6 in other areas indicate significant activity (P < 0.05) and are shown in bold. BA = Brodmann area. *Data from six scannings.

### Table 5 Heat pain on the paretic leg

<table>
<thead>
<tr>
<th></th>
<th>S.E.</th>
<th>D.R.</th>
<th>J.B.</th>
<th>I.G.</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
</tr>
<tr>
<td>S2</td>
<td><strong>3.9</strong> (–56, –28, 24)</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td><strong>4.7</strong> (–56, –32, 16)</td>
</tr>
<tr>
<td>IC</td>
<td>&lt;3</td>
<td><strong>3.7</strong> (–44, 4, 0)</td>
<td>&lt;3</td>
<td><strong>3.3</strong> (–38, 2, 6)</td>
</tr>
<tr>
<td>ACC</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td><strong>6.6</strong> (–6, –10, 48)</td>
</tr>
<tr>
<td>Other activated areas</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td><strong>5.1</strong> (–14, 44, 40; BA 31)</td>
</tr>
</tbody>
</table>

Peak t-values and stereotaxic coordinates (within parentheses, see Tables 1 and 4 for explanation) are shown for different patients and brain regions. t-Values in bold indicate significant activity (P < 0.05). BA = Brodmann area. *Data from six scannings.

### Table 6 Heat pain on the left leg in normals

<table>
<thead>
<tr>
<th></th>
<th>H.B.*</th>
<th>C.J.</th>
<th>B.J.</th>
<th>S.J.</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 (contra)</td>
<td><strong>6.0</strong> (8, –46, 74)</td>
<td>&lt;3</td>
<td><strong>7.7</strong> (12, –32, 66)</td>
<td><strong>9.7</strong> (18, –26, 56)</td>
</tr>
<tr>
<td>S2 (contra)</td>
<td><strong>4.6</strong> (52, –26, 22)</td>
<td>3.5 (34, –22, 22)</td>
<td><strong>6.1</strong> (46, –24, 16)</td>
<td><strong>6.0</strong> (36, –26, 16)</td>
</tr>
<tr>
<td>IC (contra)</td>
<td><strong>6.3</strong> (36, 10, 6)</td>
<td><strong>6.0</strong> (42, 10, –6)</td>
<td><strong>5.5</strong> (32, 26, 2)</td>
<td><strong>8.2</strong> (42, 8, 4)</td>
</tr>
<tr>
<td>ACC (contra)</td>
<td><strong>7.2</strong> (8, –6, 38)</td>
<td><strong>5.3</strong> (4, 22, 42)</td>
<td><strong>8.0</strong> (4, –6, 46)</td>
<td><strong>11.3</strong> (2, –8, 46)</td>
</tr>
<tr>
<td>S2 (ipsi)</td>
<td>3.1 (–58, –34, 24)</td>
<td>&lt;3</td>
<td><strong>4.2</strong> (–62, –24, 20)</td>
<td><strong>7.7</strong> (–46, –30, 16)</td>
</tr>
<tr>
<td>IC (ipsi)</td>
<td><strong>6.1</strong> (–34, 8, 10)</td>
<td><strong>5.5</strong> (42, 14, –2)</td>
<td><strong>5.5</strong> (–44, 0, 8)</td>
<td><strong>8.5</strong> (–44, 8, –4)</td>
</tr>
<tr>
<td>ACC (ipsi)</td>
<td><strong>6.5</strong> (4, 6, 42)</td>
<td>&lt;3</td>
<td><strong>5.7</strong> (–12, –8, 48)</td>
<td><strong>8.2</strong> (–10, 10, 36)</td>
</tr>
<tr>
<td>Other activated areas</td>
<td><strong>8.5</strong> (4, –10, 68; BA 6)</td>
<td><strong>9.1</strong> (0, –20, 64; BA 6)</td>
<td><strong>7.4</strong> (16, –46, 66; BA 7)</td>
<td><strong>11.7</strong> (0, –8, 60; BA 6)</td>
</tr>
<tr>
<td></td>
<td><strong>6.2</strong> (–58, 2, 2; BA 44)</td>
<td><strong>6.7</strong> (10, –92, 10; BA 17)</td>
<td><strong>6.2</strong> (–6, –76, 40; BA 19)</td>
<td><strong>8.4</strong> (–16, –30, 64; BA 3)</td>
</tr>
<tr>
<td></td>
<td><strong>5.1</strong> (54, 8, 2; BA 44)</td>
<td><strong>6.1</strong> (–16, –48, 68; BA 7)</td>
<td><strong>5.7</strong> (–48, –6, 8; BA 6)</td>
<td><strong>8.0</strong> (–14, –10, 14 thalamus)</td>
</tr>
<tr>
<td></td>
<td><strong>5.5</strong> (54, 10, 4; BA 44)</td>
<td><strong>5.7</strong> (–48, –6, 8; BA 6)</td>
<td><strong>5.5</strong> (54, 10, 4; BA 44)</td>
<td><strong>7.4</strong> (14, –10, 14 thalamus)</td>
</tr>
<tr>
<td></td>
<td><strong>5.4</strong> (26, 46, 32; BA 8)</td>
<td><strong>5.5</strong> (54, 10, 4; BA 44)</td>
<td><strong>5.4</strong> (26, 46, 32; BA 8)</td>
<td><strong>6.3</strong> (54, 4, 6; BA 44)</td>
</tr>
<tr>
<td></td>
<td><strong>5.2</strong> (14, –2, 62; BA 6)</td>
<td><strong>5.2</strong> (14, –2, 62; BA 6)</td>
<td><strong>5.2</strong> (14, –2, 62; BA 6)</td>
<td><strong>5.2</strong> (14, –2, 62; BA 6)</td>
</tr>
</tbody>
</table>

Peak t-values and stereotaxic coordinates (within parentheses, see Table 1 for explanation) are shown for different normal subjects and brain regions. t-Values ≥3.6 within S1, S2 and ACC, t-values ≥3.5 within IC and t-values ≥4.8 in other areas indicate significant activity (P < 0.05) and are shown in bold. BA = Brodmann area. *Data from four scannings.

**Localization of tactile and painful stimulation**

For both tactile and painful stimuli, all patients were 100% correct in determining which leg was stimulated. They did not report any qualitative differences in sensation for the two legs.

However, all patients had difficulties in determining whether the first or the fifth toe was stimulated by a painfully hot thermode (Fig. 6). All patients made errors on the paretic foot and J.B. and I.G. also made several errors on the nonparetic foot. Only one error was recorded for the normals (n = 7) and they all considered it an easy task.

**Discussion**

In hemispherectomized patients, brushing of the nonparetic leg activated similar cortical areas (S1 and S2) as observed in the hemisphere contralateral to the stimulation in normals. In contrast, painful heat stimulation of the nonparetic leg...
Fig. 5 Cortical activation evoked by painful stimulation on the nonparetic and paretic legs. The right side of the images corresponds to the right side of the patient and red circles indicate regions of interest. $t$-Values $\geq 3.6$ within the S2 and ACC search volumes and $t$-values $\geq 3.5$ within the IC search volume (see Methods) represent significant activity ($P < 0.05$). $t$-Values $> 5$ are indicated by white colour. The stereotaxic coordinates of the activations are indicated in Tables 4 and 5.
Evoked a weaker cortical activation than observed in the hemisphere contralateral to the stimulation in normals. Brushing as well as heat pain applied to the paretic leg, activated similar areas as for the nonparetic leg, showing that these areas (S1, S2, IC, and ACC) can be activated by ipsilateral pathways without transcallosal transfer.

**Tactile stimulation**

Generally, cortical activation was more pronounced for brushing of the nonparetic than the paretic leg, whereas the patients rated the brushing as equally intense for both legs. Such findings emphasize that absence of fMRI activation must be interpreted with caution and do not exclude stimulus-related neural activity in the region examined (Davis et al., 1998; Disbrow et al., 1998). Rather, the results show that under the same stimulation and scanning conditions, neural activity following ipsilateral stimulation was less likely to produce strong BOLD signals. One explanation of the lack of side differences in the patients’ intensity ratings may be that reorganization following brain damage resulted in the patients perceiving a weak neural activity evoked from the ipsilateral body half as being equally intense as a strong neural activity evoked from the contralateral body half. Alternatively, the relationship between neuronal excitability and synaptic input may have been altered for ipsilateral stimulation, resulting in a change in the coupling between neural activity and the BOLD signal (for a review, see Bach-y-Rita, 1990).

The ipsilateral S1 activation in two patients (Fig. 3) may represent reorganization since it was not observed in any of the normals (see Introduction). Furthermore, the spatial differences in S1 activation sites between stimulation of the paretic and non-paretic leg may contribute to the patients’ ability to discriminate side of stimulation. The level and mechanisms of this somatosensory reorganization can only be speculated, but one possibility is the potentiation, or disinhibition, of information processing in normally existing pathways (Kaas et al., 1999). Such pathways could include the spinothalamic and spinoreticulothalamic projections in the anterolateral quadrant of the spinal cord (Noordenbos and Wall, 1976). Another possibility is the growth of new connections at the level of the spinal cord, medulla or thalamus (Kaas et al., 1999). However, since the patients in this study had signs of neural damage early in life, the ipsilateral S1 input could also have been established during the development of the nervous system (Villablanca and Hovda, 2000).

Ipsilateral S2 was activated in only one of the patients (J.B.). Nevertheless, a previous study on three of our patients (I.G., D.R. and J.B.) showed that, under some conditions, ipsilateral S2 could be activated by brushing of the paretic hand (Bittar et al., 2000). Another recent fMRI study failed to observe any ipsilateral cortical activation following brushing of the hand in three patients with complete transection of the corpus callosum (Fabri et al., 1999). Since ipsilateral S2 was activated in all of the normals, our patient data support the notion that such activation is partly mediated via the corpus callosum (Forss et al., 1999; Karhu and Tesche, 1999).

The functional significance of the ipsilateral activation of S1 and S2 is not known. All patients could easily detect which leg was stimulated by the monofilament. Furthermore, in a separate psychophysical study, the patients had an almost normal capacity for touch detection without side differences, whereas they had a severe disturbance in tactile directional sensibility and touch localization on the paretic leg (Olausson et al., 1999). J.B. and I.G., who showed fMRI activation of ipsilateral S1 and S2, did not have better results than D.R. and S.E., who did not show any significant ipsilateral cortical activation.

Brushing of the nonparetic leg evoked similar activation as in the hemisphere contralateral to the stimulus in normals. This suggests that tactile information processing in the contralateral hemisphere is independent of the corpus callosum. Supporting evidence comes from the psychophysical study described above (Olausson et al., 1999). The hemispherectomized patients all had normal tactile directional sensibility and normal capacity for touch localization on the nonparetic leg, suggesting that information processing restricted to the contralateral hemisphere is sufficient for a variety of tactile sensory functions.

**Painful stimulation**

This is the first brain imaging study of nociceptive stimulation in patients with cortical brain lesions (Ingvar, 1999; Bushnell et al., 2000). It demonstrates for the first time that cortical areas typically involved in pain processing (S2, IC and ACC) could be activated by ipsilateral pathways directly from the periphery.

Generally, there were only marginal side differences in the patients’ ratings of the intensity and unpleasantness of the painful stimulus (Fig. 4) and within S2, IC and ACC

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**Fig. 6** Localization of painful stimulation. Each patient’s percentage of error in a localization task (see Methods) is shown for the nonparetic and paretic feet together with the average percentage of errors for the normal subjects (n = 7). Only one error was made by one of the normals.
there was no significant side difference in the t-values for the nonparetic and paretic legs. However, I.G. rated the unpleasantness of the pain, but not the intensity, more than twice as high on the paretic than the nonparetic leg. Pain affect is likely to be encoded in ACC (Rainville et al., 1997; Ploner et al., 1999) and I.G. also had a stronger ACC activation (as reflected by the t-values and the activated volumes) on the paretic than the nonparetic side. Despite the lack of side differences in the fMRI data, three of the patients made more errors in the localization test on the paretic than the nonparetic side (Fig. 6). Our interpretation, in agreement with other authors (Davis et al., 1998; Disbrow et al. 1998), is that the sensitivity of the BOLD technique may not be sufficient to detect small, but important, differences in cortical activation.

Painful stimulation of the nonparetic leg evoked less activation compared with the activation in the hemisphere contralateral to the stimulus in normals. It seems less likely that the weak pain activation in the patients was due to technical problems such as head movements. The fMRI data in the patients did not show signs of severe movement artefacts. In addition, the tactile activation evoked by stimulation of the nonparetic leg was equally as strong as the activation in the hemisphere contralateral to the stimulus in normals.

The weak contralateral cortical activation by pain in the patients suggests that transcallosal information transfer is more important for the experience of pain than for touch sensation (cf. above). This suggestion is corroborated by the psychophysical finding of a bilateral disturbance in pain localization for J.B. and I.G. (Fig. 6).

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References


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