Brain (2001), **124,** 2268–2277

Phantom movements and pain
An fMRI study in upper limb amputees

Martin Lotze,[1] Herta Flor,[3] Wolfgang Grodd,[2] Wolfgang Larbig[1] and Niels Birbaumer[1,4]

[1]*Institute of Medical Psychology and Behavioral Neurobiology and* [2]*Section of Experimental Magnetic Resonance Imaging of the CNS, Department of Neuroradiology, University of Tübingen,* [3]*Department of Clinical and Cognitive Neuroscience at the University of Heidelberg, Central Institute of Mental Health, Mannheim, Germany and* [4]*Department of General Psychology, University of Padua, Italy*

Correspondance to: Martin Lotze, MD, Institut für Medizinische Psychologie und Verhaltensneurobiologie, Eberhard-Karls-Universität Tübingen, Gartenstrasse 29, D-72074 Tübingen, Germany
E-mail: martin.lotze@uni-tuebingen.de

Summary
Using functional MRI, we investigated 14 upper limb amputees and seven healthy controls during the execution of hand and lip movements and imagined movements of the phantom limb or left hand. Only patients with phantom limb pain showed a shift of the lip representation into the deafferented primary motor and somatosensory hand areas during lip movements. Displacement of the lip representation in the primary motor and somatosensory cortex was positively correlated to the amount of phantom limb pain. Thalamic activation was only present during executed movements in the healthy controls. The cerebellum showed no evidence of reorganizational changes. In amputees, movement of the intact hand showed a level of activation similar to movement of the right dominant hand in the healthy controls. During imagination of moving the phantom hand, all patients showed significantly higher activation in the contralateral primary motor and somatosensory cortices compared with imagination of hand movements in the controls. In the patients with phantom limb pain but not the pain-free amputees, imagined movement of the phantom hand activated the neighbouring face area. These data suggest selective coactivation of the cortical hand and mouth areas in patients with phantom limb pain. This reorganizational change may be the neural correlate of phantom limb pain.

Keywords: limb amputation; phantom limb pain; fMRI; reorganization; imagination

Abbreviations: fMRI = functional MRI; M1 = primary motor cortex; PLP = phantom limb pain; S1 = primary somatosensory motor cortex; TMS = transcranial magnetic stimulation

Introduction
Phantom sensations are present in virtually all patients with limb amputation (Melzack, 1990). About 50–80% of all amputees develop phantom limb pain (PLP) (Sherman and Arena, 1992), which leads to permanent disability in >40% of the patients (Pezzin *et al*., 2000). The causes of painful and non-painful phantom phenomena are not known; both peripheral and central processes have been discussed (Sherman, 1997). A shift of neighbouring representational zones in the primary somatosensory cortex (S1) into the area that formerly represented the amputated extremity has been described as cortical reorganization subsequent to the amputation (Elbert *et al*., 1994). Flor and colleagues reported a strong positive correlation between the magnitude of PLP and the magnitude of cortical reorganization (Flor *et al*., 1995). The functional significance of these reorganizational changes was reported by Birbaumer and colleagues, who showed that local anaesthesia that eliminated PLP was associated with a shift of the cortical representation of the lip into a more caudal position that coincided with the lip location in S1 of the intact side (Birbaumer *et al*., 1997).

In addition to the reorganization of the somatosensory cortex, several studies have reported the reorganization of the primary motor cortex (M1) after amputation using PET, transcranial magnetic stimulation (TMS) or direct electrical stimulation of the cortex. For example, Kew and colleagues, using PET, reported that traumatic amputees showed greater regional cerebral blood flow in the deafferented cortex contralateral to the amputation during paced shoulder movements (Kew *et al*., 1994). Cohen and colleagues studied seven patients with unilateral upper limb amputation and a

© *Oxford University Press 2001*

patient with congenital absence of a hand using TMS (Cohen *et al*., 1991). Stump muscles at the amputated side showed larger contralateral M1 representation sites, larger motor evoked potentials and a greater percentage of motor neurone pool activation compared with those of the intact side. Fuhr and colleagues reported that lower limb amputees displayed a large percentage of alpha-motor neurone recruitment in the muscles ipsilateral to the stump when the optimal scalp position was stimulated by TMS (Fuhr *et al*., 1992). Pascual-Leone and colleagues reported an enlargement (progressing from 1 to 11 months after amputation) of the contralateral M1 representational maps of the lower face muscles and the biceps in a patient who underwent a traumatic arm amputation at the level of the middle upper arm compared with TMS investigation before amputation (Pascual-Leone *et al*., 1996). Ojemann and Silbergeld described a patient with a traumatic upper limb amputation who was investigated during craniotomy. When the deafferented motor cortex was stimulated, shoulder movements could be elicited in an area targeting the amputated hand. In addition, phantom sensations in the hand and arm could be elicited from the shoulder area (Ojemann and Silbergeld, 1995). Taken together, these studies suggest that the motor cortex and the somatosensory cortex are both reorganized subsequent to the amputation of an upper limb. Lotze and colleagues reported that reorganization not only in the somatosensory but also in the motor cortex is associated with the magnitude of PLP (Lotze *et al*., 1999*a*). In a functional MRI (fMRI) study, these authors showed that patients who used myoelectric prostheses extensively showed no cortical reorganization and absence of PLP in comparison with patients with little or no use of a prosthesis or who used a cosmetic prosthesis.

It has been proposed that motor imagery and motor performance are functionally related and that they activate overlapping neural structures (Jeannerod, 1994, 1995). In accordance with this hypothesis, recent studies using fMRI (e.g. Stephan *et al*., 1995; Decety, 1996; Lotze *et al*., 1999*b*) have demonstrated activation in M1 and the supplementary motor area during imagined movements in healthy persons. Patients with upper limb amputation usually show vivid representation of the arm and hand even many years after deafferentation (Berlucchi and Aglioti, 1997). Since amputees generally perceive movement of the phantom hand as real movements rather than imagined movements, it is likely that phantom movements in amputees substantially activate both M1 and S1. In an fMRI study, Ersland and colleagues reported M1 activation during imagined hand movements of an upper limb amputee (Ersland *et al*., 1996).

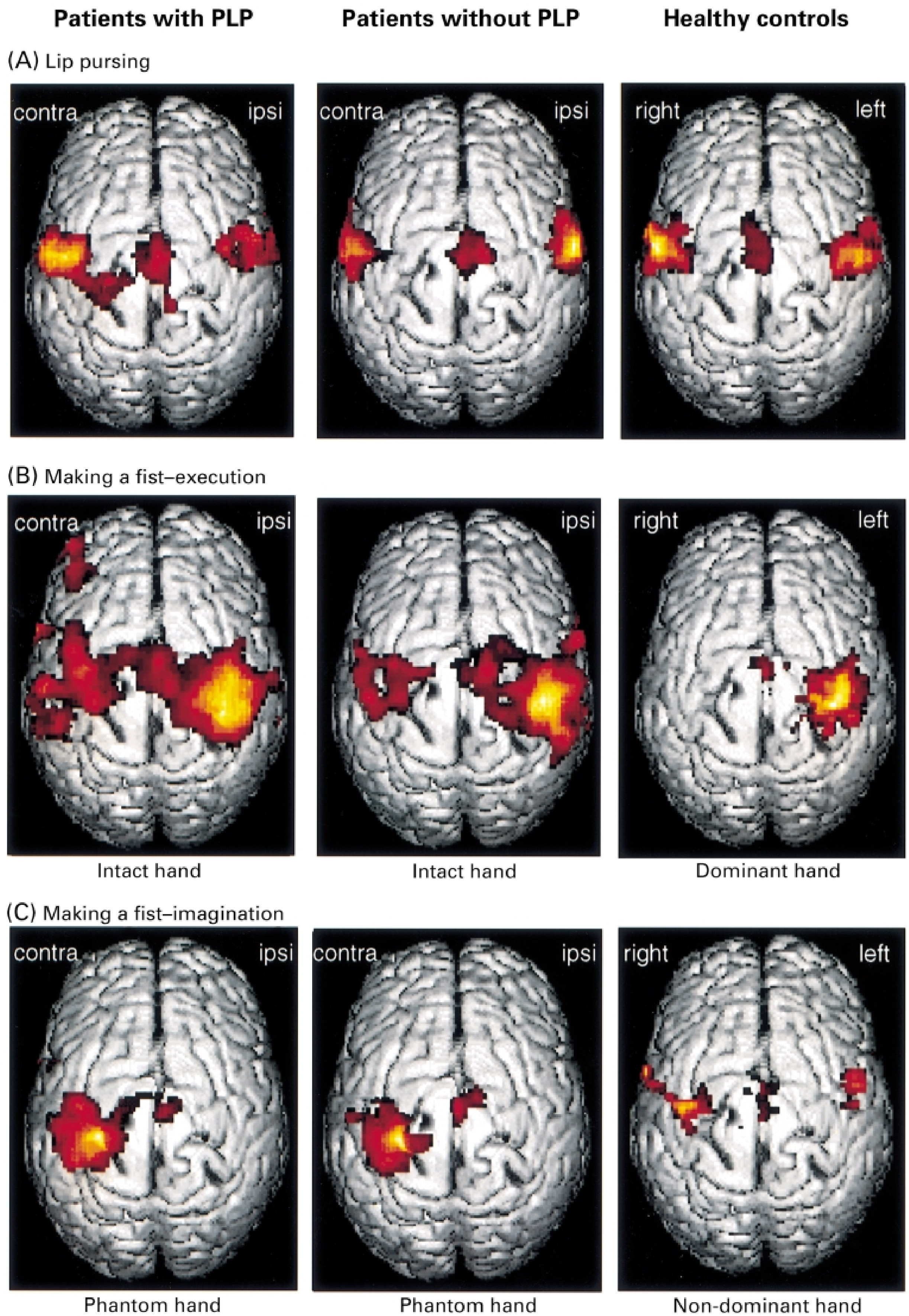
Harris proposed that PLP might be closely related to a mismatch of motor intention and proprioceptive or visual feedback (Harris, 1999). On the basis of previous findings by Fink and colleagues, who had shown that the mismatching of perceived movements of both hands, created by the use of a mirror, activated an area in the dorsolateral prefrontal cortex (Brodmann area 9/46) (Fink *et al*., 1999), Harris suggested that this region might be a cortical neural correlate of PLP. Ramachandran and Rogers-Ramachandran provided anecdotal evidence of the successful reduction of phantom sensations and PLP in upper limb amputees who observed movements of the mirrored intact hand that were perceived as movements of the phantom limb (Ramachandran and Rogers-Ramachandran, 1996).

We used fMRI during executed movements of the lip and the intact hand as well as imagined movements of the phantom hand in upper limb amputees with and without PLP. These conditions were compared with executed movements of the lip and both hands as well as imagined movements of both hands in matched healthy controls. In addition to activation in M1 and S1, activation in the posterior parietal and dorsolateral prefrontal cortex as well as subcortical structures was examined.

Methods

Subjects and procedure

Fourteen unilateral upper limb amputees (10 male; mean age 47.21 years, SD 17.54 years, range 26–78 years) participated in the study. Amputation had been performed because of an accident in 11 patients, a malignant tumour in two patients and sepsis in one patient. Nine patients had lost their dominant right hand. Time since amputation ranged from 3 to 53 years (mean 17.28 years, SD 16.45 years). Non-painful phantom limb sensations were reported by all patients at the time of the investigation. Seven patients suffered from PLP and reported PLP during the experiment. None of the patients had dorsal root lesions involved in the traumatic accident that led to the amputation. The control group consisted of seven right-handed subjects [tested with the Edinburgh Handedness Inventory (Oldfield, 1971); four male and three female; mean age 40.86 years, SD 6.23 years, range 35–52 years] with no neurological complications and of the same age as the patients [$t(17.91) = 1.21$; n.s.]. During fMRI, the patients executed movements with the intact hand and imagined movements of the amputated hand (making a fist). The controls performed both the execution and imagery tasks with the right and the left hand. To avoid muscle activity during imagery, the subjects were trained in the imagined movement task during EMG recording of the superficial upper limb flexors prior to fMRI measurement in an fMRI simulator (supine position, machine noise on tape, metronome pacing). The training was terminated when the subjects' report of vividness of imagination reached a score of 4 out of 6 (0 = no image, 6 = very vivid image) and the EMG level during imagined movements no longer exceeded the baseline level. In addition, lip-pursing movements were performed by all subjects. All movements were paced externally by a metronome at the rate of 1 Hz. Imagined movements were performed at the rate of 0.5 Hz since the frequency of 1 Hz was too fast for imagery. The experimental scanning paradigm consisted of 48 measurements in a block design. After a resting period, during which six scans were


Patients with PLP
Patients without PLP
Healthy controls
(A) Lip pursing
contra
ipsi
contra
ipsi
right
left
(B) Making a fist–execution
contra
ipsi
ipsi
right
left
Intact hand
Intact hand
Dominant hand
(C) Making a fist–imagination
contra
ipsi
contra
ipsi
right
left
Phantom hand
Phantom hand
Non-dominant hand

made, repeated movements were performed during the next six scans. These rest and activation periods alternated four times in each condition. Demographic and clinical characteristics of the patients are presented in Table 1.

Prior to fMRI data acquisition, the participants signed an informed consent form and were trained as described. The study conformed with the Declaration of Helsinki and was approved by the local ethics committee of the Medical Faculty at the University of Tübingen.

fMRI measurement

fMRI was performed with a Siemens 1.5 T scanner, using echoplanar imaging of the whole brain [matrix 96 × 128, FOV (field of view) 250 mm, TE (echo time) 59 ms, scan time 6.4 s] with 36 slices of 3 mm thickness and 1 mm gap. Forty-eight whole-brain maps (units of six measurements each during movement and rest, alternating four times) were made per condition. Additionally, T_1-weighted anatomical data sets [FLASH; effective thickness 1.5 mm, matrix 224 × 256, FOV 250 mm, TR (repetition time) 9.7 ms] were obtained. The subjects were lying supine with their eyes closed in the scanner with the head and the proximal limb securely fixed to minimize involuntary movement. Images were acquired with the improved storage system described by Klose and colleagues (Klose *et al*., 1999).

Assessment of imagery and phantom phenomena

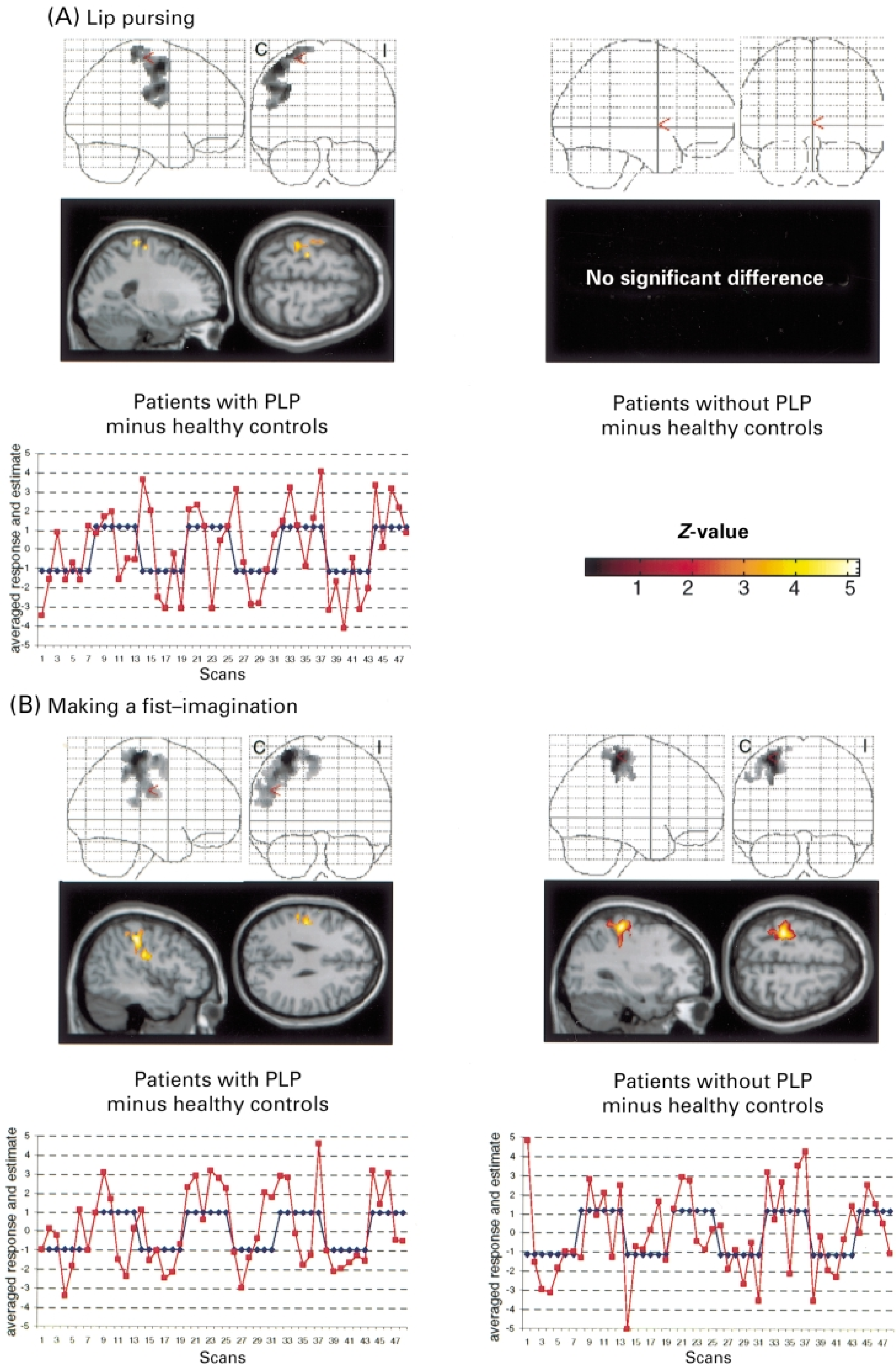
Vividness of imagination was evaluated during training and after measurement in the scanner on a seven-point rating scale (Questionnaire of Mental Imagery: 0 = no imagination, 6 = very vivid imagination (Sheehan, 1967)]. Phantom limb (PLP) and stump pain as well as non-painful phantom and stump phenomena were assessed with a seven-point scale (0 = no pain, 6 = unbearable pain) directly before scanning. All patients participated in a comprehensive Phantom and Stump Phenomena Interview (Flor *et al*., 1995).

Table 1 *Individual data for the patients and averages for controls*

Subject	Side of amputation	Age (years)	Amputation	Years since amputation	PLP*	Vividness of IM†	*Z*-value EM‡	*Z*-value IM‡	*Z*-value lip ipsi‡	*Z*-value lip contra‡
1	Right	35	Traumatic	19	0	0	3.8	0	4.1	4.1
2	Right	26	Traumatic	9	0	4	7.3	4.4	5.5	6.2
6	Right	32	Traumatic	7	0	4	5.9	6.0	4.9	5.0
11	Right	60	Tumour	7	0	1	7.4	3.8	5.3	4.6
12	Right	66	Traumatic	15	0	5	4.7	7.4	3.9	3.8
13	Right	35	Sepsis	3	0	3	6.8	4.7	7.4	7.1
14	Left	62	Traumatic	48	0	0	2.7	0	3.1	3.0
5	Right	78	Traumatic	53	1.8	2	5.8	5.8	6.6	6.4
3	Left	31	Traumatic	11	2.1	3	5.2	5.1	4.6	6.9
10	Right	63	Tumour	3	2.6	2	7.7	4.1	5.5	6.6
7	Left	28	Traumatic	3	3	6	7.6	3.8	6.9	6.1
4	Right	58	Traumatic	27	3.5	6	4.3	4.4	5.3	4.5
8	Left	31	Traumatic	7	3.7	5	6.7	7.2	6.8	6.7
9	Left	56	Traumatic	30	4.3	4	6.0	4.7	4.5	5.7
Patient group average		47.2	–	17.3	1.5	3.2	5.7	4.4	5.4	5.5
SD		17.5		16.5	1.7	1.9	1.8	2.2	1.2	1.3
Control group average		40.9	–	–	0	3.8	5.1	3.0	3.6	3.7
SD		6.2				0.7	0.9	2.1	0.8	0.7

*PLP intensity was based on the MPI Pain Intensity Scale (range 0–6). †Vividness of imagined movement (IM) of phantom limb and imagined movements of controls was assessed with Bett's questionnaire (range 0–6). ‡Activation intensity expressed in *Z*-values during executed movement (EM) of the intact hand (contralateral M1/S1), imagined movement of the phantom limb (contralateral M1/S1) and lip-pursing (contra- and ipsilateral M1/S1).

Fig. 1 Group analysis (within groups) for all patients with PLP (left panels; $n = 7$), patients without PLP (middle panels; $n = 7$) and healthy controls (right panels; $n = 7$). The normalized fMRI data (cut-off threshold $P < 0.01$; corrected extent 0.05) were projected on to the Montreal brain of SPM96 (single subject). The left hemisphere of the patients is always shown contralateral to the amputation side. Therefore, left-sided amputations were *y*-flipped during the normalization process (radiological normalization). (**A**) Lip-pursing movement. Patients with PLP showed displacement of the medial border of the lip into the M1/S1 hand and arm area. (**B**) Executed hand movement. Both patient groups showed increased cortical activation in both hemispheres. (**C**) Phantom and imagined hand movement. Both patient groups showed higher activation in M1/S1 of the hemisphere contralateral to the movement imagination (contralateral to the amputation side).


(A) Lip pursing
C
I
No significant difference
Patients with PLP
minus healthy controls
Patients without PLP
minus healthy controls
averaged response and estimate
Scans
Z-value
1
2
3
4
5
(B) Making a fist–imagination
C
I
C
I
Patients with PLP
minus healthy controls
Patients without PLP
minus healthy controls
averaged response and estimate
Scans
averaged response and estimate
Scans

Statistical evaluation

The statistical parametric mapping program (SPM96, Wellcome Institute of Cognitive Neurology, London, UK) was used for data analysis. The scans of each individual were realigned to each other to correct for interscan movement artefacts. The echo planar images of each subject were coregistered to the anatomical data sets after the anterior commissure had been defined manually as the reference point. The group data were normalized according to the SPM template (voxel, 2 × 2 × 2 mm): the data were *y*-flipped for all patients with a left-handed amputation (radiological normalization), resulting in images in which the hemisphere contralateral to the amputated hand was on the right side (Figs 1–3) (Willoch *et al*., 2000). The subjects were divided into groups with ($n = 7$) and without ($n = 7$) PLP. The echoplanar imaging data were smoothed with a 6 mm Gaussian filter (full-width at half-maximum). Using a fixed-effects test, statistically significant differences between movement and rest were assessed with the delayed box-car model. T-maps were transformed to Gaussian *t*-maps using a voxel-by-voxel *t*-to-*Z* probability transformation (Worsley *et al*., 1992). For statistical testing of significant activations corrected for the whole brain volume, a combined test of the peak intensity and the spatial extent of activation was performed (Poline *et al*., 1997). For the within-group analysis, the height threshold was set at $P < 0.01$ ($u = 2.33$) and the corrected spatial extent threshold at $P < 0.05$ (resulting in an average cut-off of 303 voxels; Fig. 1). For the between-group analysis, the intensity threshold was set at $P < 0.05$ ($u = 1.64$) and the corrected spatial extent threshold at $P < 0.05$ (resulting in an average cut-off of 748 voxels; Fig. 2). Since the activation sites in the basal ganglia, the thalamus and the cerebellum were expected to be too small to be detected with the spatial Bonferroni correction used in SPM, we employed no additional spatial threshold ($P < 0.01$ non-corrected; Fig. 3). The activation intensity of anatomically defined areas was assessed using the *Z*-value (maximal *Z*-value of a cluster within an anatomical structure). This was assumed to be more appropriate than the magnitude difference because it also considers the variance of the signal. For the comparison of activation intensities with clinical data, Pearson correlations were computed for normally distributed data and Spearman correlations for non-normally distributed data. Differences in activation intensity between the groups were evaluated with the *t*-tests or the Mann–Whitney *U*-test (non-normal data). The location of activation maxima was highly automated using SPM96 and distances in one spatial direction were calculated by simple subtraction. For the 3D evaluation of differences in representation maxima, Euclidean distances between the patient groups (in all spatial coordinates, $x1$, $y1$, $z1$) and the controls ($x0$, $y0$, $z0$) were calculated using the formula:

$$\sqrt{[(x1 - x0)^2 + (y1 - y0)^2 + (z1 - z0)^2]}.$$

Results

Lip movement

Both the patients and the healthy controls showed bilaterally represented lip movements in M1/S1. Group statistics (within groups) revealed a shift of the medial border of the lip movement representation contralateral to the amputation side into the deafferented hand area only for patients suffering from PLP (left compared with right lip; *z*-axis, PLP, 36 mm in cranial direction; no PLP, 8 mm; healthy controls, 8 mm difference) (Fig. 1A and Table 2). When difference maps for the activation in M1/S1 for the PLP patients versus the healthy controls were calculated (between-group statistics), the PLP patients showed higher activation in contralateral M1/S1 ($Z = 4.19$) and an enlarged mouth representation that extended into the former hand area (activation maximum at –42, –8, 56) (Fig. 2). This difference was not significant for the patients with non-painful phantom phenomena. No other cortical region showed a significant group difference.

Thalamic activation was observed in the controls but not in the patients (within-group statistics) (Fig. 3, right). Cerebellar representation maxima in the hemisphere ipsilateral to the amputation side were not different between the patient groups and the healthy controls (Euclidean distances: ipsilateral hemisphere, PLP, 2.82 mm; no PLP, 2.82 mm) (Fig. 3, bottom).

Executed hand movements

During the execution of movements of the intact hand, all upper limb amputees and all control subjects showed significant activation in the contralateral M1 and S1 hand areas (for group statistics within groups, see Fig. 1B). Statistics in the controls (within groups) revealed that movement of the dominant right hand showed greater M1/

Fig. 2 Differences between the groups shown in Fig. 1 were compared with a cut-off of $P < 0.05$ and an additional spatial extent threshold of $P < 0.05$. The glass brain is shown at the top of each panel and below it is the overlay on the single-subject brain that was nearest to the template used for normalization. The left hemisphere of patients is always shown contralateral to the amputated side and compared with the right hemisphere of the healthy controls. The graphs at the bottom of each statistical map illustrate the averaged response (red) and the estimate (blue) curve for the contrasts between the groups. (**A**) Lip-pursing movement. *Left*: Compared with healthy controls, patients with PLP showed increased activation in the M1/S1 hand and lip area contralateral to the amputation side. *Right*: patients without PLP showed no significant differences from healthy controls. (**B**) Imagined hand movement. *Left*: compared with healthy controls, patients with PLP showed increased activation in the M1/S1 hand and the lip area contralateral to the amputation side. *Right*: patients without PLP showed increased activation in the M1/S1 hand area when compared with healthy controls.

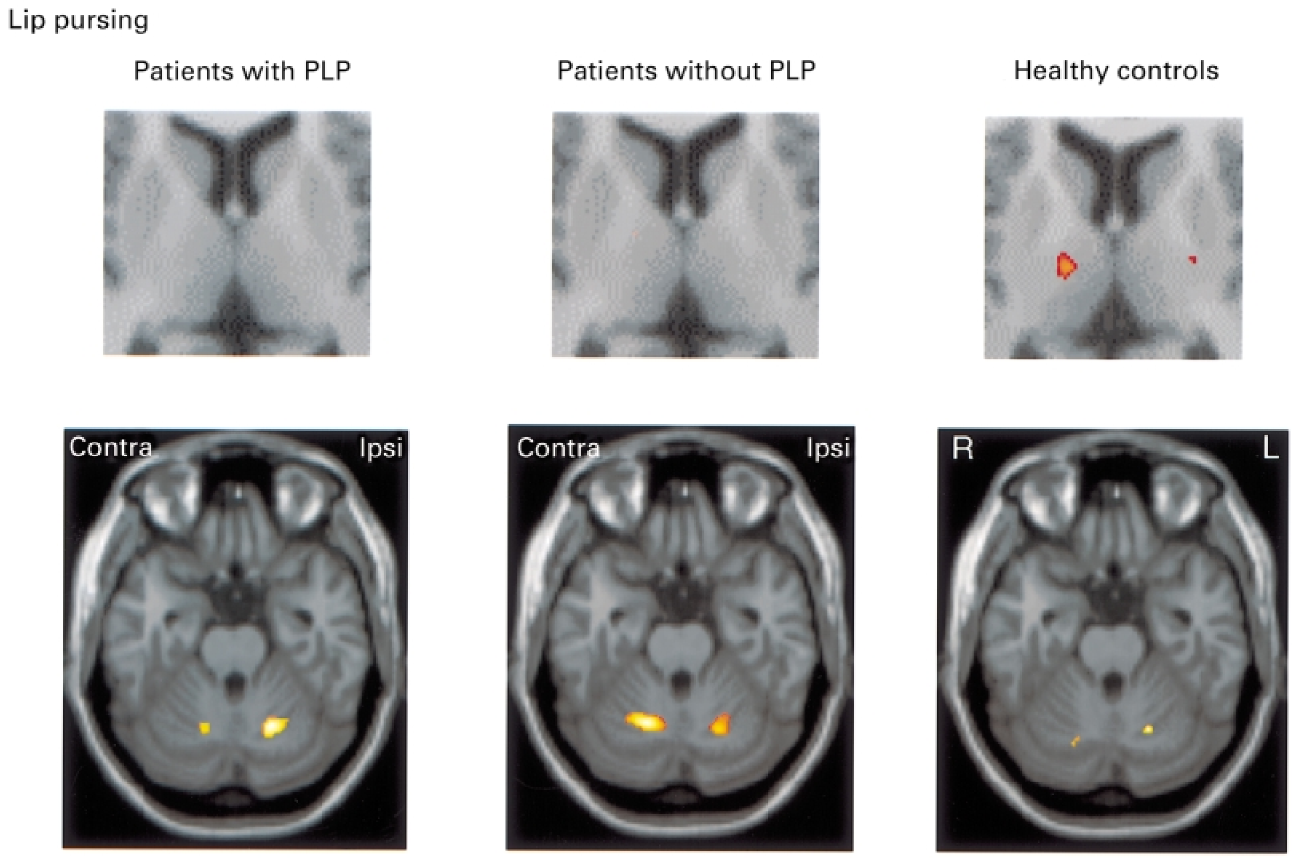


Fig. 3 Group analysis (within groups) during lip movement: thalamic (*top*; coordinates 0, 0, 0) and cerebellar activation (*bottom*; coordinates 20, –60, –26) with an intensity cut-off of $P < 0.01$ without further extent threshold (10 voxels). Only healthy controls (right) showed bilateral thalamic activation during lip movement. Cerebellar representation sites were not displaced in the patient groups compared with the healthy controls.

Table 2 *Activation sites in the whole brain*

	Lip		Executed hand movement M1/S1 ipsilateral to amputation	Imagined hand movement M1/S1 contralateral to amputation
	M1/S1 contralateral to amputation	M1/S1 ipsilateral to amputation		
Patients with PLP				
Z-value	6.79	6.11	8.07	6.50
Coordinates	–44, –12, 54	50, –8, 36	36, –24, 62	–34, –32, 56
Patients without PLP				
Z-value	6.63	7.01	7.79	5.68
Coordinates	–52, –8, 38	62, –8, 34	42, –26, 44	–30, –32, 56
Controls				
Z-value	6.53	6.77	6.97	4.23
Coordinates	–58, –14, 40	52, –8, 36	24, 20, 52	–38, –24, 48

Contralateral for patients means right for healthy controls; ipsilateral for patients means left for healthy controls.

S1 activation intensity (average $Z = 5.07$) than movement of the non-dominant hand [average $Z = 4.40$; $t(19) = 2.11$, $P < 0.05$]. Compared with movement of the left hand in healthy controls, movement of the intact hand in the amputees showed higher contralateral M1/S1 activation [$t(10.12) = 3.00$, $P < 0.01$]. When contralateral M1/S1 activation of the intact hand in the amputees was compared with contralateral activation in the controls during right-hand movement, the difference was not significant [$t(18) = 1.69$].

Imagined hand movements

All amputees showed increased contralateral M1/S1 activation in the hand area compared with the controls (Fig. 1C). This difference was significant for patients with and without PLP compared with the healthy controls (for between-group statistics, see Fig. 2B). However, only patients with PLP showed increased activation in the M1/S1 lip area contralateral to the amputation side (coordinates –46, –18, 28; $Z = 3.34$) (Fig. 2B). Four healthy subjects displayed significant contralateral activation in the M1 hand area during the imagined movement task with the right or left hand (individual statistics). In contrast, 11 out of 14 amputees produced significant contralateral M1 activation during imagined movements. Vividness of imagery was not significantly different between the patient groups and the healthy controls [$F(2, 20) = 1.08$]. Vividness score in the pain-free patients was 2.21 (SD = 2.07), in patients with PLP it was 4.00 (SD = 1.73) and in the healthy controls it was 3.80 (SD = 0.70). Vividness of imagination was positively correlated with contralateral M1/S1 activation intensity during imagined movements for amputees ($r = 0.67$; $P < 0.01$), but not when the healthy controls were included ($r = 0.31$; not significant).

Discussion

In the present study, executed lip and intact hand movements and movements of the phantom limb were examined in upper limb amputees using fMRI and were compared with executed lip and hand and imagined hand movements in healthy controls. Reorganization of S1 and M1 into the deafferented hand area from the lip area was only observed in patients who had PLP. This has been reported previously for the somatosensory domain (Flor *et al.*, 1995, 1998, 2000; Birbaumer *et al.*, 1997; Montoya *et al.*, 1998) and is now extended to the motor cortex.

Although extensive cortical reorganization was observed in the present study, it was not associated with increased activation of the thalamus. Activation in the thalamus was only observed in the healthy controls. It has been proposed that the pain experienced during traumatic limb deafferentation may modulate reorganization in cortical areas (S1/M1) via thalamocortical pathways (Knecht *et al.*, 1998*a*). Our results do not support the assumption that patients with PLP show enhanced thalamic activity that is then reflected in cortical reorganization (see also Ergenzinger *et al.*, 1998; Flor *et al.*, 2000). Recent PET data comparing PLP patients in hypnotically induced painful compared with painless phantom limb positions suggest a significant relationship of induced pain with activation in the thalamus (Willoch *et al.*, 2000). Differences in results concerning the thalamus between the present study and the study of Willoch and colleagues are probably due to methodological factors: fMRI shows less sensitivity in the thalamus (but may show more sensitivity in other regions) than PET, which may result in a lack of significant differences in the between-group comparison of PLP patients with controls within this region (Jueptner and Weiller, 1998). In the within-group statistics of the patient group with PLP, the difference with respect to pain intensity between the activation and resting periods may be too small to evoke a significant increase in thalamic activation.

A comparison of executed hand movements of the intact hand in the amputees with movement of the right or left hand in the healthy controls revealed evidence for use-dependent plasticity. The amount of activation in contralateral M1/S1 in relation to movements of the intact hand in the amputees was similar to the activation caused by movement of the dominant hand in the healthy controls. When the non-dominant hand in the healthy controls was used for this comparison, movement of the intact hand in the amputees showed significantly higher activation irrespective of the side of the intact hand. These findings are similar to those of Elbert and colleagues, who used neuromagnetic source imaging and reported an expansion of the cortical representation of the intact hand in upper limb amputees compared with healthy controls (Elbert *et al.*, 1997).

During imagined movements of the phantom hand, all amputees showed significantly higher activation in the contralateral M1/S1 hand area than the healthy controls. Twelve out of 14 amputees spontaneously reported a feeling of actual movement of the phantom hand when they were asked to imagine movements. Accordingly, M1/S1 activation increased with increasing vividness of the perceived phantom movement. This may be related to a high degree of attention to the phantom limb (Berlucchi and Aglioti, 1997). To control for this attentional factor, a comparison of the PLP patients with patients suffering from acute or chronic pain might be useful.

In the patients with PLP, imagined movement of the phantom also activated the cortical mouth representation. This co-activation was probably due to the high overlap of the hand, arm and mouth representations that is generally observed during sensory stimulation in amputees with PLP (e.g. Kew *et al.*, 1994; Flor *et al.*, 1995). This co-activation is also reflected in the fact that stimulation of the mouth area often activates phantom sensations in the amputated arm or hand (Ramachandran *et al.*, 1992). Since imagery seems to activate the same brain regions as actual perception or movement, this overlap is also present during imagined movements and may be viewed as an additional indicator of cortical reorganization in PLP patients (Doetsch, 1998). We did not observe significant activation in Brodmann areas 46/9, which is postulated to be indicative of PLP (Harris, 1999), in any of the amputees. Distortion of the perceived body image was also described in healthy subjects by Lackner when muscle vibrations were applied to generate proprioceptive misinformation (Lackner, 1988). Referred sensation has also been reported after sequential painful and non-painful stimulation of the hand and mouth region (Knecht *et al*., 1998*b*). In both instances, painful sensations were not reported. Thus, there is so far no corroborative evidence for the assumption of Harris.

The results of the present study suggest that reorganization in M1/S1 contralateral to the amputation side is the main neural correlate of PLP. This finding was present not only when lip movements were examined but also for imagined movements of the phantom hand.

Acknowledgements

We would like to thank two anonymous reviewers for very helpful suggestions on the revision of the manuscript. This investigation was supported by Volkswagen-Stiftung and Deutsche Forschungsgemeinschaft.

References

Berlucchi G, Aglioti S. The body in the brain: neural bases of corporeal awareness. [Review]. Trends Neurosci 1997; 20: 560–64.

Birbaumer N, Lutzenberger W, Montoya P, Larbig W, Unertl K, Topfner S, et al. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. J Neurosci 1997; 17: 5503–8.

Cohen LG, Bandinelli S, Findley TW, Hallett M. Motor reorganization after upper limb amputation in man. Brain 1991; 114: 615–27.

Decety J. Do imagined and executed actions share the same neural substrate? [Review]. Brain Res Cogn Brain Res 1996; 3: 87–93.

Doetsch GS. Perceptual significance of somatosensory cortical reorganization following peripheral denervation. [Review]. Neuroreport 1998; 9: R29–35.

Elbert T, Flor H, Birbaumer N, Knecht S, Hampson S, Larbig W, et al. Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. Neuroreport 1994; 5: 2593–7.

Elbert T, Sterr A, Flor H, Rockstroh B, Knecht S, Pantev C, et al. Input-increase and input-decrease types of cortical reorganization after upper extremity amputation in humans. Exp Brain Res 1997; 117: 161–4.

Ergenzinger ER, Glasier MM, Hahm JO, Pons TP. Cortically induced thalamic plasticity in the primate somatosensory system. Nat Neurosci 1998; 1: 226–9.

Ersland L, Rosen G, Lundervold A, Smievoll AI, Tillung T, Sundberg H, et al. Phantom limb imaginary fingertapping causes primary motor cortex activation: an fMRI study. Neuroreport 1996; 20: 207–10.

Fink GR, Marshall JC, Halligan PW, Frith CD, Driver J, Frackowiak RS, et al. The neural consequences of conflict between intention and the senses. Brain 1999; 122: 497–512.

Flor H. The functional organization of the brain in chronic pain. In: Sandkühler J, Bromm B, Gebhart GF, editors. Nervous plasticity and chronic pain. Amsterdam: Elsevier; 2000. p. 313–22.

Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995; 375: 482–4.

Flor H, Elbert T, Mühlnickel W, Pantev C, Wienbruch C, Taub E. Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. Exp Brain Res 1998; 119: 205–12.

Fuhr P, Cohen LG, Dang N, Findley TW, Haghighi S, Oro J, et al. Physiological analysis of motor reorganization following lower limb amputation. Electroencephalogr Clin Neurophysiol 1992; 85: 53–60.

Harris JA. Cortical origin of pathological pain. Lancet 1999; 354: 1464–6.

Jeannerod M. The representing brain: neural correlates of motor intention and imagery. Brain Behav Sci 1994; 17: 187–245.

Jeannerod M. Mental imagery in the motor context. [Review]. Neuropsychologia 1995; 33: 1419–32.

Jueptner M, Weiller C. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. Brain 1998; 121: 1437–49.

Kew JJ, Ridding MC, Rothwell JC, Passingham RE, Leigh PN, Sooriakumaran S, et al. Reorganization of cortical blood flow and transcranial magnetic stimulation maps in human subjects after upper limb amputation. J Neurophysiol 1994; 72: 2517–24.

Klose U, Erb M, Wildgruber D, Muller E, Grodd W. Improvement of the acquisition of a large amount of MR images on a conventional whole body system. Magn Reson Imaging 1999; 17: 471–4.

Knecht S, Henningsen H, Höhling C, Elbert T, Flor H, Pantev C, et al. Plasticity of plasticity? Changes in the pattern of perceptual correlates of reorganization after amputation. Brain 1998a; 121: 717—24.

Knecht S, Soros P, Gurtler S, Imai T, Ringelstein EB, Henningsen H. Phantom sensations following acute pain. Pain 1998b; 77: 209–13.

Lackner JR. Some proprioceptive influences on the perceptual representation of body shape and orientation. Brain 1988; 111: 281–97.

Lotze M, Grodd W, Birbaumer N, Erb M, Huse E, Flor H. Does the use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? Nature Neurosci 1999a; 2: 501–2.

Lotze M, Montoya P, Erb E, Hülsmann E, Flor H, Klose U, et al. Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. J Cogn Neurosci 1999b; 11: 491–501.

Melzack R. Phantom limbs and the concept of a neuromatrix. [Review]. Trends Neurosci 1990; 13: 88–92.

Montoya P, Ritter K, Huse E, Larbig W, Braun C, Topfner S, et al. The cortical somatotopic map and phantom phenomena in subjects with congenital limb atrophy and traumatic amputees with phantom limb pain. Eur J Neurosci 1998; 10: 1095–102.

Ojemann JG, Silbergeld DL. Cortical stimulation mapping of phantom limb rolandic cortex. Case report. J Neurosurg 1995; 82: 641–4.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9: 97–113.

Pascual-Leone A, Peris M, Tormos JM, Pascual AP, Catala MD. Reorganization of human cortical motor output maps following traumatic forearm amputation. Neuroreport 1996; 7: 2068–70.

Pezzin LE, Dillingham TR, MacKenzie EJ. Rehabilitation and the long-term outcomes of persons with trauma-related amputations. Arch Phys Med Rehabil 2000; 81: 292–300.

Poline JB, Worsley KJ, Evans AC, Friston KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. Neuroimage 1997; 5: 83–96.

Ramachandran VS, Rogers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. Proc R Soc Lond B Biol Sci 1996; 263: 377–86.

Sheehan PW. A shortened form of Betts' questionnaire upon mental imagery. J Clin Psychol 1967; 23: 386–9.

Sherman RA. Phantom pain. New York: Plenum Press; 1997.

Sherman RA, Arena JG. Phantom limb pain: mechanisms, incidence and treatment. Clin Rev Phys Rehabil Med 1992; 4: 1–26.

Stephan KM, Fink GR, Passingham RE, Silbersweig D, Ceballos-Baumann O, Frith CD, et al. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. J Neurophysiol 1995; 73: 373–86.

Willoch F, Rosen G, Tölle TR, Oye I, Wester H-J, Berner N, et al. Phantom limb pain in the human brain: unraveling neural circuitries of phantom limb sensations using positron emission tomography. Ann Neurol 2000; 48: 842–9.

Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain. J Cereb Blood Flow Metab 1992; 12: 900–8.

Received March 19, 2001. Revised May 4, 2001.
Accepted June 14, 2001