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# Plasticity of plasticity?
## Changes in the pattern of perceptual correlates of reorganization after amputation

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## Summary
*We report a follow-up study on seven arm amputees in whom magnetic source imaging had originally revealed a strong correlation between the amount of cortical invasion of the deafferented cortex and the amount of pain evoked sensation mislocalized to the phantom limb. This re-examination was performed in order to corroborate the phenomenon of mislocalization. On follow-up examination for mislocalization 4 weeks later, a close correlation had remained between the original amount of cortical representational reorganization of the amputation zone (at the first examination) and the number of sites from where painful stimuli evoked sensations referred to the phantom limb, i.e. the amount of perceptual mislocalization, at the second examination. However, contrary to our expectation, the topography of referred sensation had completely changed in every patient. These results suggest that while the overall extent of reorganization is a rather stable phenomenon, the concomitant changes in the pattern of sensory processing are not. This may be due to the fact that alterations of sensory processing are not hardwired, but are rather mediated by an extensive and interconnected neural network with fluctuating synaptic strengths. This mechanism may be of importance for neurological rehabilitation.*

**Keywords**: plasticity; somaesthesia; perceptual mislocalization; referred sensation; magnetic source imaging

## Introduction
A referred sensation is a sensation that is perceived to be emanating from a body site other than the one that was stimulated. This is frequently observed after limb amputation (Cronholm, 1951) where somaesthetic stimulation is sensed not only at the stimulation site, but is often referred or mislocalized to a phantom limb as well.

With the demonstration of massive shifts of cortical representational zones following upper extremity deafferentation in monkeys (Pons *et al.*, 1991) and amputation in humans (Elbert *et al.*, 1994; Yang *et al.*, 1994) this phenomenon has received increased attention as a possible perceptual correlate of the cortical reorganization that occurs after amputation (Ramachandran *et al.*, 1992). Noninvasive neuroimaging techniques such as magnetic source imaging provide a measure of the reorganization of neural activity, but they do not, of themselves, indicate the relevance of these changes to the perceptual experience or behaviour of the individual. Appropriately designed studies of referred sensation after amputation are important in that they offer the opportunity to obtain suggestive evidence concerning the possible relationship between cortical and perceptual reorganization. These two processes can serve as a model for the potential of cortical reorganization for the recovery of function after cerebral damage in neurological rehabilitation.

In a previous series of studies we had investigated the neurophysiological and perceptual changes associated with cortical reorganization after amputation (Elbert *et al.*, 1994; Flor *et al.*, 1995; Knecht *et al.*, 1995, 1996*a*, *b*; Taub *et al.*, 1995). A significant relationship was established between the expansion of representational fields with intact sensory input into the neighbouring deafferented cortex area as revealed by magnetic source imaging, and (i) the amount of phantom limb pain experienced by the amputees and (ii) the number of locations from which painful stimuli could evoke sensations referred to the phantom limb (Knecht *et al.*, 1996*a*; Flor *et al.*, 1995). However, no distinct topographic relationship

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emerged between the sites on the body from which stimulation evoked mislocalizations and the sites on the phantom limb where referred sensations were perceived. To ascertain whether mislocalization after amputation was a stable phenomenon we therefore re-examined the pattern and extent of mislocalization after 4 weeks, and in one case again after >1 year.

## Methods

### *Subjects*

We studied nine patients, all male with a mean age of 60 years (range 32–74 years). Four of them had amputations on the left side and five on the right; five had upper and four lower arm amputations. Amputation had taken place between 10 and 42 years prior to this study (mean 19.5 years). In two patients the amputation was related to an osteosarcoma and in the rest to accidents. All subjects had phantom sensations. One of the nine patients declined a magnetoencephalographic examination. Another patient, who had been evaluated with evoked magnetic fields, was not available for follow-up examination, reducing the number of patients with magnetic source imaging and sensory reassessment to seven. Patients gave informed consent to participate in the study, which was approved by the ethical committee of the University of Munster, Germany.

### *Sensory evaluation*

All evaluations of referred sensation were carried out by the same examiner (C.H.). The first assessment was performed on the same day as the magnetic source imaging. The second examination for referred sensation was conducted on the average 4 (range 3–6) weeks later. One subject (T48) was re-examined a third time, after 1.5 years, by another examiner (S.K.). In all subjects, 30 bilateral standardized body sites were stimulated: 10 on the face, 10 on the ventral trunk and 10 on the back and the legs. During stimulation subjects were asked ‘What do you perceive while you are being stimulated at this location?’. When subjects reported referred sensation in their phantom limb, four more sites at a distance of 3 cm medial, lateral, caudal and cranial to the first location were stimulated. The stimulation was performed in four different modalities: (i) touch was elicited by a cotton applicator; (ii) vibration was induced with a 256-Hz tuning fork; (iii) pain was evoked by a light pin prick of ~1-s duration; and (iv) heat was applied by a thermode at 40°C. One stimulus in each modality was applied per site. Since pin prick and thermode application also activate touch receptors, sites where the application of the pin or the thermode evoked the same sensation as the cotton applicator were not considered pain or heat-specific points. After completion of the stimulation, all sites from which referred sensations had been elicited were stimulated again in a random order to test for consistency (brief retesting). The locations of the stimulation sites and the locations of corresponding perceived sensation sites on the phantom limb were recorded on templates. No attempt was made to quantify the size of the phantom limb. On follow-up examinations stimulation sites were relocated by following the preset anatomical landmarks, e.g. on the upper border of the eyebrow in the midline or immediately lateral to the nostrils in the upper nasolabial fold.

### *Magnetic source imaging*

Recording and analysis of somatosensory evoked fields was performed in the same manner as in previous studies (Elbert *et al.*, 1994, 1995; Flor *et al.*, 1995; Knecht *et al.*, 1995, 1996*a*). The dewar of a 37-channel biomagnetometer (BTi, San Diego), 14.4 cm in diameter, was placed over the parietotemporal cortex contralateral to the stimulated body sites. The tip of the first and fifth finger on the intact arm and both sides of the lower lip were stimulated 1000 times at an average rate of 2 Hz with non-noxious tactile stimuli applied by a pneumatic device. Response data from an interval of –100 ms to + 250 ms relative to the stimulation were sampled at 520.5 Hz, digitally filtered with a bandpass of 0.01–100 Hz (second-order zero-phase shift Butterworth filter, 12 dB per octave) and averaged after rejection of runs exceeding 2 pT in any of the recording channels.

The averaged evoked responses were source-analysed using the single equivalent current dipole model in a spherical volume conductor (Sarvas, 1987). The exact position of the dewar with respect to the head and the individual head shape was determined using a sensor position indicator (a device that measures the position in three-dimensional space). This device also served to determine the individual head shape. For each subject, a local sphere was fitted to this digitized head shape. The origin of this coordinate system was set at the midpoint of the medial–lateral axis (*y*-axis) which joined the centre points of the entrance to the acoustic meati of the left and the right ears (positive towards the left ear). The posterior–anterior axis (*x*-axis) was oriented from the origin to the nasion (positive towards the nasion) and the inferior–superior axis (*z*-axis) was perpendicular to the *x*–*y* plane (positive towards the vertex).

The response peak was determined by the maximal field power (measured as root-mean-square across the 37 channels) of calculated dipoles with a goodness of fit of >0.95 and a confidence volume smaller than 300 $cm^3$ within the latency range from 35 to 75 ms after stimulus onset.

Invasion of the cortical amputation zone (that had represented the now-absent limb) was assessed in the following way: The centre of responsivity for stimulation of the intact hand (the mean of the locations of the representation of the first and fifth digits in the contralateral primary somatosensory cortex) was projected across the midline of the brain onto the hemisphere representing the amputated side. This procedure is said to produce a ‘mirror image’ of the location of the cortical representation of the intact hand

in the cortex opposite the amputation (Elbert *et al.*, 1994). In a previous control study on healthy volunteers (Knecht *et al.*, 1996*a*) representations of both hands had proved to be symmetrical within a limit of 0.1 ± 0.5 (SD) cm. In amputees, the distance was then calculated between the projected representation of the intact hand and the lip representation on the amputated side. This value was subtracted from the corresponding distance in the hemisphere representing the intact side; the resulting difference served as the measure of reorganizational invasion.

## Results

On both the first and the second examination, stimulation in each of the somaesthetic modalities tested resulted in sensation referred to the phantom limb in at least some individuals. Results from stimulation in single modalities are illustrated in Fig. 1 for two patients (T58, T48). Points from which mislocalization could be elicited were located ipsilateral and contralateral to the amputation side. They involved the face, the ventral trunk and the opposite shoulder. In neither of the examinations was an exact topographic mapping detected involving a strict one-to-one relation between a stimulation point and a distinct point in the phantom limb as reported by Ramachandran and others (Ramachandran *et al.*, 1992; Halligan *et al.*, 1993).

When subjects were immediately retested at the end of the first examination, which lasted ~1 h, the pattern of referred sensation was identical to the initial results in all amputees. However, when patients were re-examined 4 weeks later, the pattern of mislocalization was not found to be the same as that observed in the first examination in any of them. Across patients and modalities the overall number of mislocalizations was insignificantly higher on the second compared with the first examination (*t* test for dependent samples with $n = 8$, $P = 0.16$). Out of 119 stimulation sites from which referred sensation was evoked in the second examination (across all subjects and modalities), only 16 (13%) had also given rise to mislocalization in the first examination (Table 1). All other stimulation sites that elicited mislocalization in either the first or the second sensory evaluation were different in the two examinations. The same held true for the third examination of one patient (T48) after >1.5 years. As indicated in the diagrams of individual cases in Fig. 1A and B, even in those few cases where stimulation of a site elicited sensations referred to the phantom in both the first and the second (or third) examination, the quality of that perception was quite variable across these examinations. For example, in subject T58 (Fig. 1B) painful stimulation at the right side of the forehead produced a sensation of intense touch in the whole phantom hand in the first examination and a sensation of pressure radiating into the phantom hand as well as a feeling of extending phantom fingers in the second examination.

The extent of cortical invasion from the lip representation ipsilateral to the amputation into the area formerly representing the now amputated hand, as determined by magnetic source imaging, varied from 0.01 to 3.86 cm. Figure 2 illustrates the extent of invasion relative to the number of sites from which mislocalizations were elicited in different modalities. Only for painful stimulation was there a close correlation of the amount of cortical invasion (as measured at the time of the first examination) with the number of mislocalizations on the first ($n = 8$, Spearman $r = 0.85$, $P < 0.01$) and the second ($n = 7$, Spearman $r = 0.73$, $P = 0.06$) examination. The total numbers of mislocalizations following painful stimulation in the first and the second examinations were also correlated ($n = 8$, Spearman $r = 0.7$, $P = 0.05$). For the number of mislocalizations following stimulation in other modalities, no relation was observed with the amount of cortical reorganization.

## Discussion

Our study revealed that the correlation between the extent of cortical representational invasion, as assessed by magnetic source imaging, and the extent of mislocalization after amputation remains stable over a period of at least 4 weeks. However, contrary to our original expectation, the pattern of referred sensation had changed within this time span in every amputee.

### *Methodological considerations*

We repeated sensory evaluation four times to test for the stability of mislocalization. Two full examinations were performed 4 weeks apart and two brief re-examinations were done within 1 h of each full examination. While the extent and pattern of referred sensations remained stable when the brief retesting was performed, this was not the case for the pattern of mislocalization after 4 weeks.

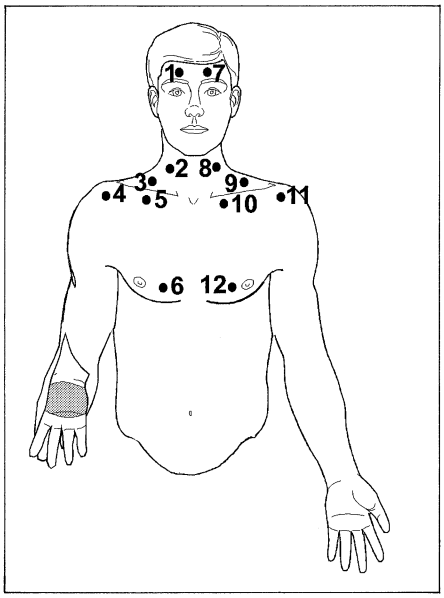
Assessment of referred sensation is not an objective procedure. Although re-examinations were conducted in an identical fashion, and by the same person, the conditons during follow-up examinations were different from those in the original ones because the patients now knew that they had referred sensations. An increased awareness of the phenomenon of referred sensation after participating in the first examination may have led them to include fainter mislocalizations which they had neglected in the first examination. This could explain why there were generally higher reports on mislocalization on the second examanition compared with the first (Table 1).

When amputees are asked to report on their phantom, they are frequently concerned about their credibility because non-affected persons occasionally ascribe phantom sensations or referred sensations to unresolved grief for the missing limb. In fact, three of our patients pointed out they were aware of discrepancies in their reports on the sites which elicited referred sensations during the first and the last testing, but stressed that they were sure of these changes. Thus, in the amputees there was no evidence for a bias toward a change

(A)

**Touch (T48)**

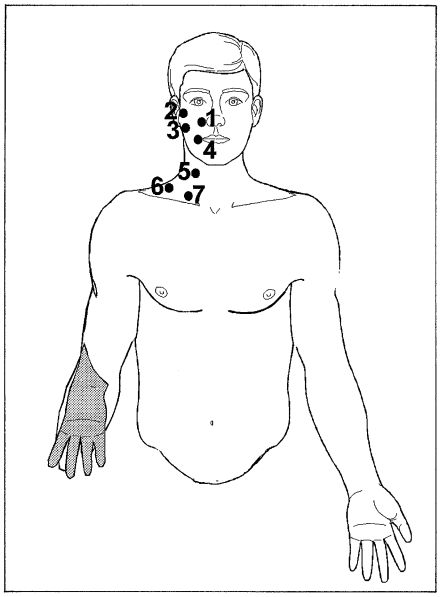
First examination




1 – 12: Sensation of mild tingling in the palm of the phantom hand (without fingers)

(B)

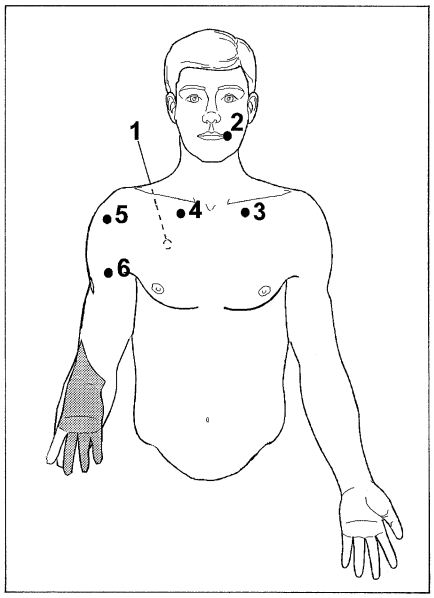
Second examination




1–4: Sensation of mild tingling in the palm of the phantom hand (from the lower arm to the tips of the fingers)
5 – 7: Sensation of intense tingling in the palm of the phantom hand (from the lower arm to the tips of the fingers)

(C)

Third examination

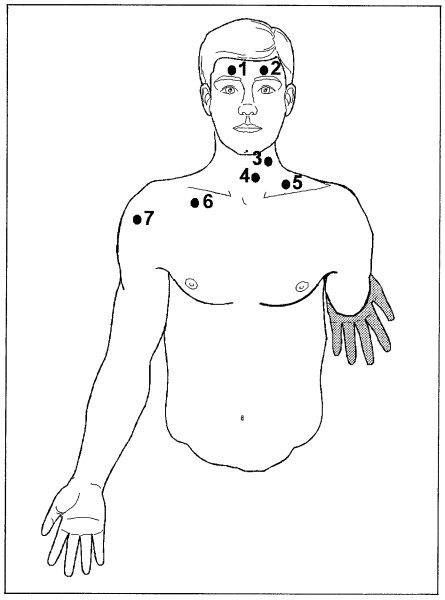



1–3: Sensation of mild tingling in the palm of the phantom hand (from the lower arm to the tips of the fingers). Site 1 is marked by a dashed line because it was located on the back rather than front of the chest.
5 – 6: Sensation of distinct and intense tingling in the palm of the phantom hand (from the lower arm to fingers III–V)

(B)

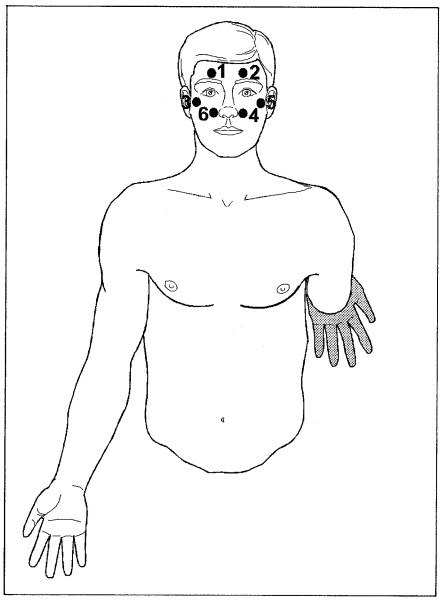
**Painful stimulation (T58)**

First examination




1: Sensation of intense touch in the whole phantom hand
2 – 7: Sensation of moderate touch in the whole phantom hand

Second examination




1: Sensation of pressure radiating into the phantom hand; additionally sensation of extension of all phantom fingers
2 – 4: Sensation of pressure radiating into the phantom hand
5 – 6: Sensation of pressure radiating into the phantom hand; additionally sensation of mild pain in the whole phantom hand

**Fig. 1** Examples of mislocalization to the phantom limb (shaded area) on the first, the second and the third examinations in Patient T48 following touch stimulation (**A**), and on the first and second examinations in Patient T58 following painful stimulation (**B**).

**Table 1** Number of sites which gave rise to mislocalizations in the first and the second examinations and (identically) in both examinations

| Subject | Touch stimuli | | | Vibration | | | Heat stimuli | | | Pain stimuli | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exam. 1 | Exam. 2 | Both | Exam. 1 | Exam. 2 | Both | Exam. 1 | Exam. 2 | Both | Exam. 1 | Exam. 2 | Both |
| T59 | 0 | 10 | 0 | 2 | 9 | 2 | 0 | 0 | 0 | 2 | 4 | 0 |
| T41 | 0 | 6 | 0 | 2 | 7 | 1 | 1 | 5 | 0 | 0 | 0 | 0 |
| T47 | 2 | 5 | 1 | 1 | 10 | 0 | 0 | 0 | 0 | 0 | 5 | 0 |
| T50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| T49 | 3 | 10 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 10 | 3 |
| T48 | 12 | 7 | 2 | 5 | 7 | 1 | 0 | 0 | 0 | 4 | 7 | 0 |
| T39 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 5 | 1 |
| T58 | 8 | 5 | 2 | 2 | 0 | 0 | 7 | 0 | 0 | 7 | 6 | 2 |
| Totals | 25 | 44 | 6 | 12 | 33 | 4 | 8 | 5 | 0 | 23 | 37 | 6 |

in the pattern of referred sensation. In the examiner there was no such bias either, given our original prediction of stable mislocalizations.

## *Extent of perceptual changes*

We have not addressed the issue as to what extent cortical reorganization is stable over time, as assessed by magnetic source imaging. However, preliminary data from neuromagnetic and neuroelectric recordings (S. Grüsser, W. Mühlnickel, D. Schachinger and H. Flor, unpublished results) suggest that the invasion into the vacated cortical representational zones after amputation is a very robust phenomenon. Cortical reorganization after amputation is highly correlated with the number of sites from where painful stimuli evoke sensations referred to the phantom limb, i.e. the extent of mislocalization (Knecht *et al.*, 1996*a*). In keeping with these data we found a continued high correlation between the original magnitude of cortical invasion on magnetic source imaging and the extent of mislocalization after 4 weeks. We cannot rule out the possibility that the increase in the absolute number of mislocalizations from painful stimuli on the second evaluation could be accompanied by an increased cortical representational invasion. However, as was pointed out before, an increased attentiveness for the phenomenon seems a more plausible explanation for the different numbers of painful mislocalizations on the first and second examinations.

Based on the high correlation between cortical reorganization and phantom pain, Flor *et al*. (1995) and Taub *et al.* (1995) have suggested that the barrage of nociceptive inputs following deafferentation might be related to the magnitude of invasion of the vacated cortical representational zone. Spitzer *et al*. (1995) proposed that cortical reorganization may be maintained by randomly occurring inputs from the amputation site or the corresponding spinal dorsal horn, that would lead to a persistent activation in the vacated cortical space. Given that the patients we followed were suffering, to variable extents, from continuing phantom pain, the suggested mechanisms could well explain why the correlation between mislocalization of nociceptive stimuli and the amount of cortical invasion remained the same for at least 4 weeks.

## *Pattern of perceptual changes*

Magnetoencephalographic sources represent the sum total of synchronously activated cortical neurons. The magnitude of representational shifts on magnetic source imaging differentiates amputees with few mislocalizations of painful stimuli from those with many mislocalizations. The pattern of referred sensation, however, depends on the specific synaptic connectivity within a somatosensory pathways rather than the sum total of neuronal activation. Like the first examination the follow-up investigation did not reveal a strict topographical matching between stimulation sites and points of referred sensation as reported in some other studies (Ramachandran *et al.*, 1992; Halligan *et al.*, 1993, 1994). In these earlier studies fewer points were tested than in our investigation; this could increase the chance of obtaining a pattern that roughly matches the topography of an amputated limb. Conversely, with 30 sites and four different modalities evaluated in our study, topographical inconsistencies were seen not only on testing within one modality but additionally between modalities.

The somatosensory cortex is characterized by dense intracortical connections (Jones and Powell, 1970). Additionally, there seems to be a wide divergence of afferent projections. Microneurographic studies indicate that the activity in a single peripheral somatosensory fibre, in the absence of lateral competition, can project to a cortical area almost as extensive as that of the whole peripheral nerve, which comprises several thousands of afferent fibres (Kunesch *et al.*, 1995). Furthermore, magnetoencephalographic studies show that cutaneous information in humans can even access the ipsilateral primary somatosensory cortex (Schnitzler *et al.*, 1995). Conversely, a single cortical neuron can receive convergent inputs from different body sites (Smits *et al.*, 1991). This anatomical convergence of somatosensory projections is reflected by occasional perceptual errors in humans, i.e. by mislocalization or referred sensations. Although mostly seen in amputees (Cronholm, 1951), it has

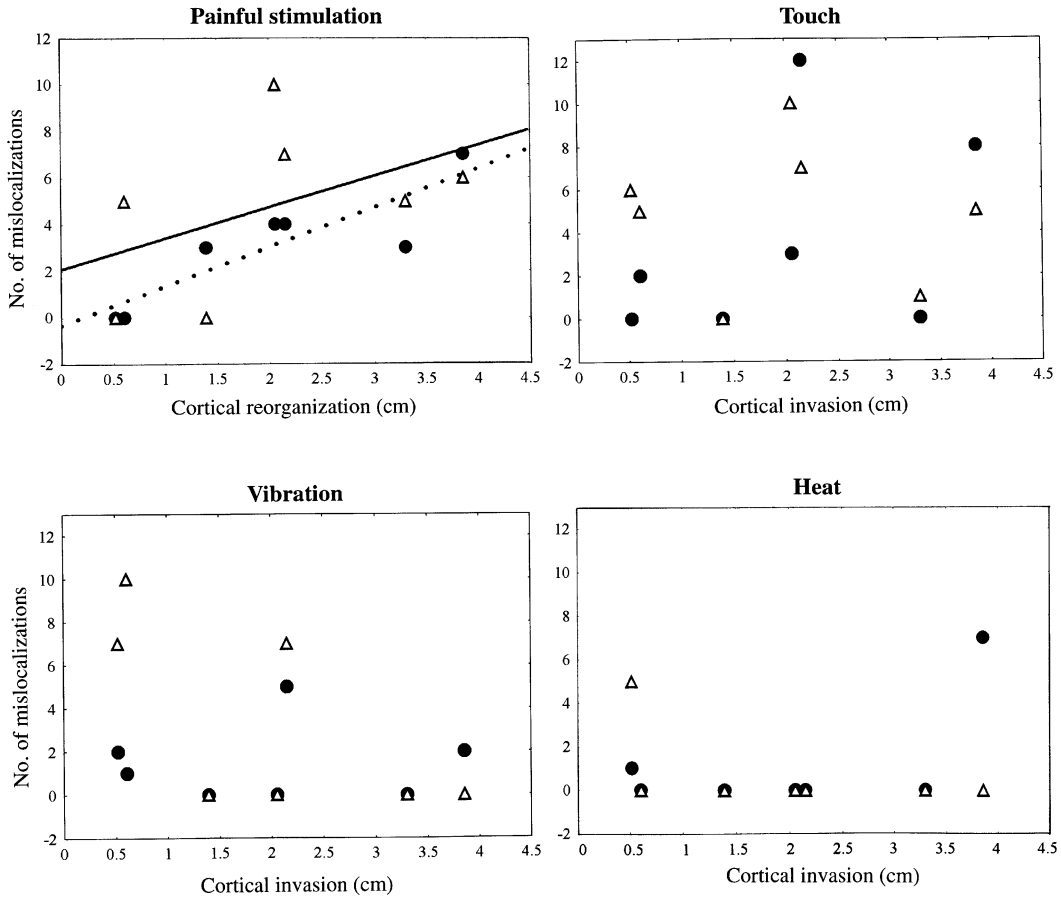



**Fig. 2** The relationship between cortical invasion on magnetic source imaging (horizontal axis) in single amputees and the number of mislocalizations on the first and the second sensory examination from stimulation in different modalities (vertical axis). Regression lines are shown for the pain modality (continuous and dotted lines for the first and second examinations, respectively). Closed circles = first examination; open triangles = second examination.

occasionally been observed in healthy subjects (Richter, 1977) and in patients suffering from chronic pain (Katz and Melzack, 1987).

Given the evidence for divergent and convergent somaesthetic input to the cortex, mislocalization could be viewed as the unmasking of connections which are usually inhibited or subthreshold for perception and which are inaccurate with respect to the conventional homuncular organization suggested by Penfield and Rasmussen (1950). Mislocalization can also occur after peripheral nerve damage when the peripheral nerve begin to sprout. This mislocalization gradually subsides when patients use the affected limb again and relearn, by behavioural strengthening, to localize somatosensory information accurately. Limb amputation, however, deprives the cortex of somaesthetic input without replacement by behaviourally relevant afferent information and stabilization of somatosensory processing. Our data suggest that, in the absence of behavioural strengthening, the synaptic efficacies of subthreshold divergent connections, which give rise to a particular pattern of sensory processing, are not stable over an extended period of time. Since our patients reported consistent mislocalizations 1 h after the first examination, the time required for such a mechanism to become effective seems to be at least 1 h and may, in fact, be up to 4 weeks, as in our series, or even longer. Thus, in a single case study Halligan and colleagues found the pattern of mislocalization in their patient to be consistent after 6 weeks (P. W. Halligan, personal communication) but disorganized on follow-up examination after 1 year (Halligan *et al.*, 1994).

Since different somaesthetic modalities are processed in different pathways and cortical fields (Head, 1918; Jones and Friedman, 1982; Knecht *et al.*, 1996*b*), we tested for referred sensation following painful, touch, vibration and thermal stimulation. In all modalities stimulation produced mislocalization. The extent of mislocalization to painful stimulation correlated best with the extent of invasion on magnetic source imaging on both examinations. This may be due to the fact that nociceptive processing itself is subject to modulations of central excitability (Hillman and Wall, 1969; Cook *et al.*, 1987) and that the mechanisms may be similar to those that influence the extent of cortical invasion on magnetic source imaging. The perceived modality of referred sensation frequently differed from the modality of stimulation (Fig. 1A and B). Mostly, the referred sensation in the phantom limb was felt as a tingling or a pressure. Therefore,

reorganized sensory processing seems to be inaccurate, not only with respect to localization but also with respect to modality.

Research in animals and humans has shown that the network of highly interconnected somatosensory neurons allows for learning of sensorimotor tasks and relearning of function after damage (Jenkins and Merzenich, 1987; Recanzone *et al.*, 1992*a*; Pascual-Leone and Torres, 1993; Pascual-Leone *et al.*, 1995). Differential and contextually relevant stimulation of a subset of afferents can increase their functional synaptic effectiveness and thereby stabilize functionally meaningful processing (Merzenich *et al.*, 1988; Recanzone *et al.*, 1992*b*). Assuming that mislocalization in amputees represents an unmasking of latent projections, the fact that sensations can be referred from body sites remote and even contralateral to the amputation demonstrates the extent and potential of cortical interconnections. In the undisturbed state these connections may serve the acquisition of sensorimotor skills that involve coupling of information from remote points of the peripheral receptor sheet. In the disturbed state, i.e. after peripheral or central damage, the interconnections probably constitute a major basis for rehabilitation. As our study shows, the processing patterns in the reorganized network are extensive, inaccurate and highly fluctuating rather than hardwired. However, behavioural strengthening of relevant patterns in this sensory network could allow for recovery of function.

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