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Reorganizational and perceptional changes after amputation

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Summary

The demonstration of cortical representational shifts in adult animals subsequent to deafferentation from amputation or dorsal rhizotomy has spurred attempts to elucidate the perceptual correlates of reorganization. Because the hand is flanked by the face and the trunk on the cortical homunculus it has been suggested that cortical remapping in arm amputees leads to a mislocalization of sensations from these sites to the phantom arm in a systematic manner with modality specific one-to-one topographical correspondence. Therefore, we assessed shifts of representational zones by magnetic source imaging in eight arm-amputees and examined them for referred sensation by somaesthetic stimuli of different modalities at standardized sites. It was found that referred phantom sensations can be evoked from sites on the face and the trunk ipsilateral but also contralateral to the amputation and that the extent of physiological reorganization as revealed by magnetic source imaging strongly correlates with the number of sites, be it ipsi- or contralateral, from where painful stimuli evoke referred sensation. Thus, it seems that the extent of reorganization after amputation is closely related to nociceptive inputs. The mislocalization evoked from both sides of the body, suggesting involvement of bilateral pathways, demonstrates that the perceptual changes go beyond what can be explained by shifts in neighbouring cortical representational zones.

Keywords: plasticity; reorganization; pain; amputation; somaesthetic

Introduction

After amputation, most patients report sensations that seem to emanate from the lost body part. This effect has been termed phantom sensation (Mitchell, 1871; Carlen *et al.*, 1978; Shukla *et al.*, 1982; Jensen *et al.*, 1983). For most amputees the phantom is only mildly distracting (Sherman and Sherman, 1992). However, in some, the sensations are very intense and painful. Phantom sensations can occur spontaneously or they can follow environmental changes (Arena *et al.*, 1989; Frank and Lorenzoni, 1992) or stimulation of other body parts (Katz and Melzack, 1987).

Cronholm (1951) and Ramachandran *et al.* (1992*a*, *b*) have reported on upper extremity amputees in whom phantom sensation could be elicited by tactile stimulation of the face ipsilateral to the amputation. Since the map of the hand on the sensory homunculus in the cortex is flanked by the face and the trunk, Ramachandran *et al.* (1992*a*, *b*) maintained that this mislocalization was a direct perceptual correlate of an invasion of sensory inputs from these sites into the hand area as described in animal experiments on cortical plasticity by Merzenich *et al.* (1984) and Pons *et al.* (1991). Moreover, Ramachandran *et al. (1992a, b)* argued that phantom sensation itself arises because somaesthetic input from the face and the trunk take over the vacated representational zone of the now missing limb. Stimulated by this suggestion, we tested whether referred sensation is a consistent sequel to amputation and can be related to cortical reorganization.

We had previously found shifts of representational areas to be related to chronic phantom pain but not to the presence or absence of mislocalization of light touch (Elbert *et al.*, 1994; Flor *et al.*, 1995; Taub *et al.*, 1995). In this study we extended the range of somaesthetic stimulation modalities employed in eight long-term arm-amputees who additionally underwent magnetic source imaging. We report that stimulation induced referred sensation is a common

Table 1 *Subject characteristics*

Subject	Site of amputation	Age (years)	Age at amputation (years)	Cause	Invasion (cm)
T39	Right hand below wrist	48	10	Accident	3.30
T41	18 cm below left shoulder	50	42	Osteosarcoma	0.52
T47	12 cm below right shoulder	70	18	Accident	0.61
T48	15 cm below right elbow	62	12	Accident	2.16
T49	19 cm below left shoulder	68	17	Accident	2.06
T50	23 cm below right shoulder	73	24	Accident	1.39
T57	15 cm below left elbow	27	21	Accident	0.01
T58	11 cm below left shoulder	31	29	Accident	3.86

phenomenon, that is related mostly to nociceptive inputs and is indicative of more extended plastic changes than have been demonstrated in cortical mapping studies. A brief report of some of these results has already appeared (Knecht *et al.*, 1995).

Methods

Eight male unilateral upper-extremity amputees participated in the study after giving informed consent. The site and cause of the amputation, present age and age at time of the amputation are shown in Table 1. All subjects had phantom limb sensation but were unaware of the phenomenon of referred sensations from stimulation of intact portions of the body. Eight healthy volunteer subjects acted as controls having also given their informed consent

Assessment of perceptual changes

Phantom limb pain was measured by a standardized pain-intensity scale, i.e. the German version (Flor *et al.*, 1990) of the West Haven–Yale Multidimensional Pain Inventory (Kerns *et al.*, 1985). Results by this assessment have previously been reported (Flor *et al.*, 1995).

An examination for referred sensation induced by somatosensory stimulation was performed on the day of the magnetic source imaging. In all subjects, 30 standardized body sites (Fig. 1) were stimulated and subjects were asked open-ended questions about what they perceived. No effort was made to direct the subjects' attention to possible sensations referred to the phantom limb. When referred sensation was reported the surrounding skin area was tested additionally at four more sites at a distance of 3 cm medial, lateral, caudal and cranial to the first spot. Four different somatosensory modalities were used: (i) touch was elicited by a cotton applicator; (ii) vibration was induced by a 256-Hz tuning fork; (iii) pain was evoked by pinprick; (iv) heat was applied by a thermode at 40°C. Since pinprick 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 sensation had been elicited were stimulated again to test for consistency.

Magnetic source imaging

Somatosensory evoked fields were elicited by non-noxious pneumatic stimulation of the tip of the first and fifth digit of the intact hand and of both corners of the mouth on the lower lip. During the recording, subjects lay in a lateral position supported by a vacuum mattress. The sequence of stimulation sites was varied according to a fixed irregular order across subjects. At each site 1000 stimuli were applied at an average rate of 2 Hz. The interval between stimulus onsets was 500±50 ms. Using a BTi Biomagnetometer (San Diego, USA), magnetic fields were recorded in a magnetically shielded room from 37 locations over a circular concave area (14.4 cm in diameter) above the parieto-temporal cortex contralateral to the site of stimulation. The dewar was centred over the points of the 10–20-system for electrode placement C3 and C4, respectively. The magnetoencephalographic data were sampled at 520.5 Hz, and responses for each stimulus (from −100 to +250 ms) were averaged and filtered digitally with a bandpass of 0.01–100 Hz (second-order zero-phase shift Butterworth filter, 12 dB/octave). A response was excluded from the average if its range exceeded 2 pT in any of the magnetometer channels. A source analysis based on the single equivalent current dipole model in a spherical volume conductor was applied to each evoked field using the mean of 20 sample points. The size of the sphere was determined by a fit to the scalp in the area of measurement. From the dipoles with a goodness-of-fit larger than 0.95 and a confidence volume smaller than 300 mm^3 within the latency range of 35–75 ms after the stimulus onset, the point in time with the maximal field power (measured as root mean square across channels) was considered as the response peak. The shift of the cortical representational zone of the face on the amputation side was assessed in the way schematically depicted in Fig. 2: the representation of the first and fifth digit of the intact hand were mirrored by projecting them into the hemisphere representing the amputated side. Then the Euclidean distance between the mirrored representation of the mean of the first and fifth digit and the representation

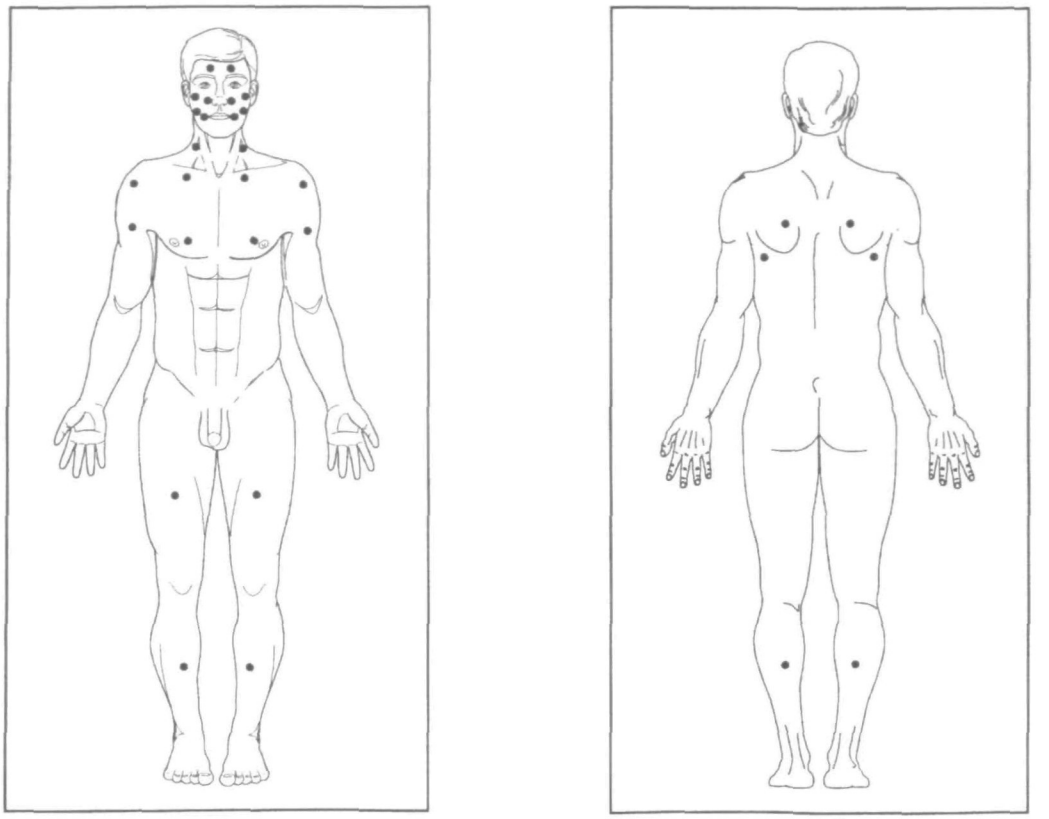

Fig. 1 Localization of 30 points which were stimulated by touch, vibration, heat and pain in all subjects to test for referred sensation in the phantom limb.

of the lip on the amputated side was calculated. This distance was compared with the corresponding distance in the other hemisphere. The difference between these distances on the amputation and on the intact side was taken as a measure of representational shift. As a control for hemispheric representational symmetry, magnetic source imaging was performed in eight healthy volunteers (age 25–40 years) in the same way as in the amputees. The hemispheric difference of the relative lip representation, i.e. the Euclidean distance between the lip representation and the mean of the first and the fifth digit on the left as compared with the right hemisphere, in this control group was 0.1 ± 0.5 cm.

Results

Referred sensation could be elicited in all but one subject. An overview of the findings is given in Table 2. Examples of stimulation in one modality in single cases are presented in Fig. 3A–C. The circumstances of stimulation leading to mislocalization were variable across subjects. Touch, vibration, heat or pain or a combination thereof brought about referred sensation. Moreover, the quality of somatosensory experience in the phantom limb frequently differed from the modality that was used for stimulation. For example, vibration or heat could similarly elicit a tingling sensation. One amputee reported the referred sensation as an experience of limb movement.

Points from which referred sensation could be elicited were located in the face and the upper part of the trunk. However, these points were located ipsi- as well as contralaterally to the amputation (34 ipsilateral, 31 contralateral). A somatotopical relationship between stimulation and perception was found in only one amputee. This was not strictly point-to-point (Fig. 3C). Type and pattern of referred sensation were always stable over several repetitions within the ~60 min long examination session. No mislocalization was reported on stimulation of the legs or the back.

Magnetic source imaging (Table 2) demonstrated reorganizational shifts of the representation area of the lip toward the hand area on the side of the amputation varying from 0.01 to 3.86 cm. No relationship could be established between cortical reorganization and a particular pattern of referred sensation. When the location of stimulation sites is disregarded and only the total number of points from which mislocalization was elicited is considered, there is a strong correlation (Spearman: $r = 0.86$, $P = 0.006$) for points of painful stimuli and the extent of cortical reorganization (Fig. 4). The extent of phantom pain as assessed by the German version of the West Haven–Yale Multidimensional Pain Inventory also showed a large significant linear relationship with the extent of representational shift

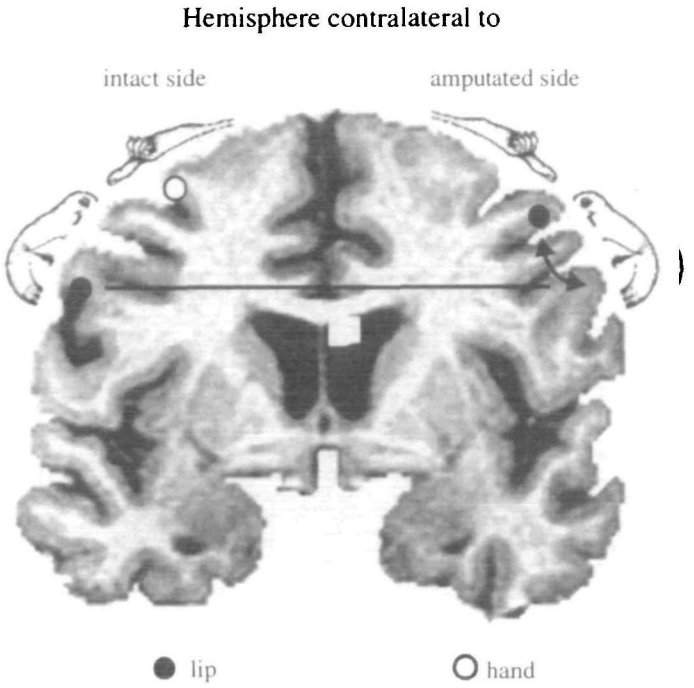

Fig. 2 Schematic presentation of the way the shift of the lip representation on the amputation side relative to the intact side (i.e. the hemisphere contralateral to the respective side) was determined. The central sulcus is actually oriented somewhat diagnonal to this coronal scan. Note that the direction of the shift is toward the former homuncular localization of the limb that was amputated.

(Spearman: $r = 0.89$, $P = 0.003$) (Fig. 4). The total number of sites from which painful stimuli evoked mislocalization and the amount of phantom pain showed a significant positive correlation as well (Spearman: $r = 0.77$, $P = 0.025$) (Fig. 4).

Discussion

Our results show that after limb amputation the orderly cortical remapping demonstrated by magnetic source imaging is not translated into a similarly ordered set of perceptual changes.

Four major observations were made in the present study: (i) referred sensation in amputees can be evoked by different somatosensory modalities and from sites contra- as well as ipsilateral of the amputation; (ii) the mode of stimulation seldom coincides with the perceived somaesthetic modality in the phantom; (iii) the greater the cortical reorganization after amputation the more likely painful stimuli will be mislocalized into the phantom limb; (iv) the more likely patients will suffer from phantom pain.

Non-nociceptive pathways

We did not find in any of the eight subjects that mislocalization of either painful stimuli or nonpainful stimuli as touch or vibration had a significant same-modality or one-to-one topographic correspondence with the eliciting stimuli. This suggests that the observation of Ramachandran *et al.* (1992*a*, *b*) and Halligan *et al.* (1993) of this type of remapping represents a relatively rare event. The pneumatic stimulation used as the basis of our magnetic source imaging was nonpainful. Therefore, the shifts of cortical representational areas we observed should have been a result of changes in non-nociceptive pathways. However, we did not observe any particular relationship of cortical reorganization to the pattern of tactile mislocalization, and tactile stimulation was the main modality employed in the facial remapping experiments of other investigators (Ramachandran *et al.*, 1992*a*, *b*; Halligan *et al.*, 1993). To summarize, the present findings do not support Ramachandran's attractive hypothesis that referred sensation is a direct perceptual correlate of cortical reorganization. In the present series we also did not find a significant correlation between the total number of sites from which nonpainful stimulation evoked referred sensation and the extent of cortical reorganization. This may be due to the limited sample size. However, even with this number of subjects a significant correlation with painful stimuli could be established. This suggests that nociceptive perceptual phenomenona predominate.

Nociceptive pathways

In keeping with findings in monkeys (Merzenich *et al.*, 1984; Pons *et al.*, 1988) and humans (Yang *et al.*, 1994) we have earlier demonstrated massive cortical reorganization in arm-amputees (Elbert *et al.*, 1994) and have furthermore found a

Table 2 *Number of sites from where referred sensation was evoked*

Subject	Invasion	Phantom pain	Touch			Vibration			Heat			Pain		
			Total	Ipsilat.	Contralat.	Total	Ipsilat.	Contralat.	Total	Ipsilat.	Contralat.	Total	Ipsilat.	Contralat.
T57	0.01	0	0	0	0	0	0	0	0	0	0	0	0	0
T41	0.52	1.33	0	0	0	2	2	0	1	1	0	0	0	0
T47	0.61	0	2	2	0	1	1	0	0	0	0	0	0	0
T50	1.39	3.00	0	0	0	0	0	0	0	0	0	3	3	0
T49	2.06	2.33	3	0	3	0	0	0	0	0	0	4	0	4
T48	2.16	2.67	12	6	6	5	5	0	0	0	0	4	0	4
T39	3.30	4.67	0	0	0	0	0	0	0	0	0	3	0	3
T58	3.86	4.70	8	6	2	2	0	2	7	3	4	7	4	3

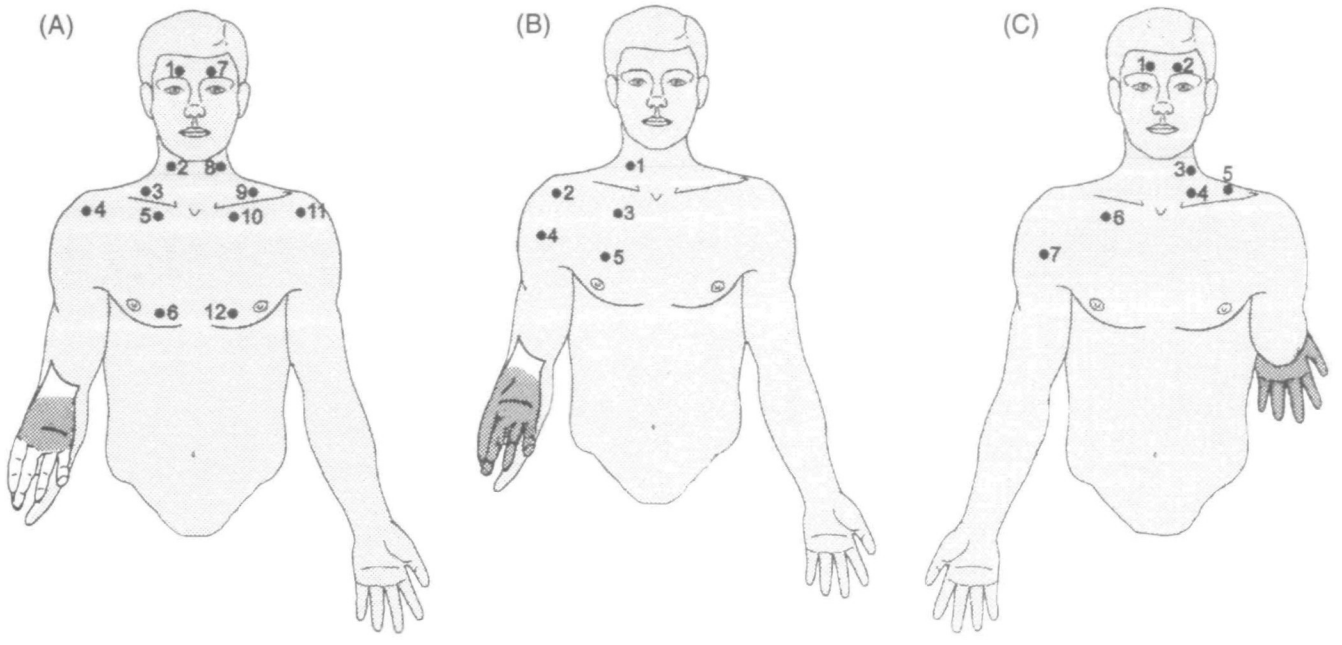

Fig. 3 Schematic drawing of the pattern of referred sensation in Subject T48 to stimulation by touch (sites 1–12 gave tingling sensation in the palm of the phantom) (**A**) and vibration (vibration of sites 1–5 produce 'vibration' of the whole phantom hand) (**B**) and in Subject T58 to stimulation by pain at the sites indicated (**C**). Pain stimulus at site 1 gave sensation of intense touch and at sites 2–7 gave a sensations of moderate touch in the whole phantom hand.

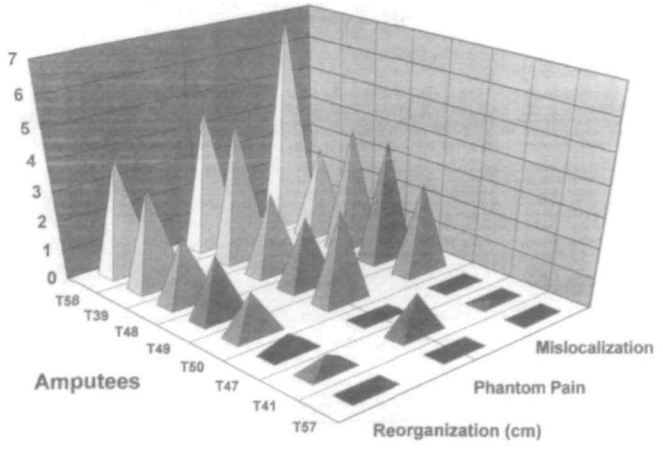

Fig. 4 Correlation between shift of cortical representational zones on magnetic source imaging (reorganization), the amount of phantom pain and the number of ipsi- and contralateral sites from where painful stimuli evoked referred sensation in the phantom limb (mislocalization): (i) Spearman correlation between reorganization and phantom pain: $r = 0.89$, $P = 0.0034$; (ii) Spearman correlation between reorganization and mislocalized painful stimuli: $r = 0.86$, $P = 0.006$; (iii) Spearman correlation between phantom pain: $r = 0.77$, $P = 0.025$.

strong correlation between the extent of plastic changes and the amount of chronic phantom pain (Flor *et al.*, 1995). The consequences of deafferentation on the pain system have previously been studied in animals. Long-term dorsal rhizotomies in monkeys have been shown to result in a transneuronal degeneration of non-nociceptive somatosensory pathways with a concomitant increase of activity in thalamic cells innervated by pain afferents (Rausell *et al.*, 1992). Mislocalization of painful stimuli in our patients with large reorganizational shifts is consistent with these findings and could be explained by an imbalance of nociceptive and non-nociceptive inputs with a lasting hyperexcitability of nociceptive pathways after amputation. This hyperexcitability could contribute to mislocalization of transmission of signals from neighbouring or diffusely projecting pathways associated with the reorganization. Since pain has widespread bilateral projections, involvement of nociceptive afferents could explain why referred sensation was elicited by painful stimuli contralateral as well as ipsilateral to the amputation (Knecht *et al.*, 1996). In fact, it is possible that a considerable amount of referred sensation is relayed by the nociceptive system since low level excitation of some nociceptive afferents can mediate nonpainful sensations which are generally found hard to describe and are frequently referred to as 'pricking' or 'unpleasant' (Jyvasjarvi and Kniffki, 1987; Handwerker and Kobal, 1993). These sensations, labelled 'prepain' (Brown *et al.*, 1985), bear some resemblance to the reports on referred sensation in our subjects and to descriptions by previous authors dating back to 1733 (Hales, 1733). Such a mechanism would explain some of the incongruency between physical stimulation type and the perceived somatosensory attributes of referred sensation.

Anatomical considerations

One-third of the routinely tested stimulation sites in the study was on the legs and the back locations whose thalamic and suprathalmic afferents do not immediately flank the arm

pathways as do those associated with the face and trunk. No referred sensation was elicited from either the legs or the back. Thus, mislocalization seems to be related to somatotopically adjacent pathways. However, in ~40% of all cases mislocalization was elicited from sites contralateral to the amputation (Table 2). In considering this effect it should be born in mind that apart from bilateral nociceptive pathways plastic changes can involve various cerebral structures. For example, it is known that reorganization can take place in SII (Pons *et al.*, 1988). Since this area receives bilateral projections, plastic changes in SII could account for the fact that mislocalization was elicited by stimulation from points contra- as well as ipsilateral to the amputation. The same may hold true for other areas receiving bilateral input and for the primary somatosensory cortex which has transcallosal reciprocal connections to the contralateral homotopic areas (Jones *et al.*, 1975; Schnitzler *et al.*, 1995). Calford and Tweedale (1990) have demonstrated that plastic changes in the primary somatosensory cortex opposite a peripheral denervation are mirrored acutely by corresponding changes in the opposite hemisphere. They suggest that interhemispheric pathways have a role in maintaining balance between corresponding cortical fields. They could also be involved in an interhemispheric transfer of referred sensation.

Mechanisms

The shifts in cortical somatosensory representational zones found in humans in magnetic source imaging studies using contralateral nonpainful stimulation (Elbert *et al.*, 1994; Yang *et al.*, 1994; Flor *et al.*, 1995) accord with results from intracortical recordings in animals (Merzenich *et al.*, 1984; Pons *et al.*, 1991). Magnetic source localization based on dipole location conveys no information about the size of the area actually generating the neuromagnetic field. However, analogous to the results from animal studies, it is likely that the shifts of the lip dipole source in our study actually represent an extension rather than a complete shift of the lip area into the hand area. This would explain why touch to the lip is still accurately localized and why intrafascicular microstimulation in patients with amputated fingers evokes sensations in the phantoms similar to that in healthy subjects (Schady *et al.*, 1994). The perceptual changes resulting from stimulation on both sides of the body noted here, however, go beyond what could be expected from simple field expansion and suggest that extended and bilateral pathways are reorganized after amputation. Whether perceptual changes in amputees, as contrasted with evoked responses, are mediated by nociceptive and non-nociceptive or only nociceptive inputs remains an issue requiring further research. The fact that nonpainful sensations can be elicited by nociceptive afferents (Handwerker and Kobal, 1993) makes the resolution of this issue difficult.

Magnetic source imaging, unlike invasive intracortical recording, is but one rather gross measure of the transmission of somatosensory input to the cortex. Subtle changes may go undetected. Thus we did not find any relationship between reorganization and age or extent of the amputation. However, the close correlation of the extent of reorganization on this gross scale with the amount of phantom pain and with the likelihood of mislocalization of painful stimuli points to an important role of pain in reorganization. It is of note that expansion of cortical fields and referred sensation can also be found in nonamputated chronic pain patients (Katz and Melzack, 1987; Flor *et al.*, 1993). Whether functional reorganization is a cause or a consequence of pain, or whether both are consequences of yet another unknown mechanism remains to be established. One conceivable mechanism is that pain is the initial event. As is often the case in amputations and with considerable differences between amputees, pain can arise by continuous discharges from lacerated peripheral nociceptive fibres in the traumatized limb. The demonstration of hyperactive cells in the spinal cord after nerve section suggests that chronification of this pain can occur by spinal reorganization (Asada *et al.*, 1990). It could be speculated that this continuous nociceptive firing then lowers the thresholds of cortical neurons leading to an activation by formerly subthreshold latent afferent projections. This, in turn, could increase representational field sizes and lower the perceptual thresholds for somaesthetic afferents with extensive cortical projections. In this way representational shifts and mislocalizations could be explained by the same mechanism.

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