

## Increased excitability in the primary motor cortex and supplementary motor area in patients with phantom limb pain after upper limb amputation

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### Abstract

Using functional magnetic resonance imaging and single slice FLASH technique, we investigated reorganization of the hand representation of the primary sensorimotor cortex (SMC) in 16 patients with upper extremity amputation. Patients were asked to perform finger tapping with the intact hand, repetitive eye closing and anteflexion of the amputation stump or intact shoulder. Six normal volunteers served as control. In the normal volunteers activations during shoulder anteflexion, finger tapping and eye closure were located within the central sulcus in a medio-lateral fashion. Patients demonstrated invasion of the face or shoulder representation into the hand representation of the amputated limb. Eight phantom limb pain patients showed significantly greater activation in SMC and supplementary motor area (SMA) in contrast to eight patients without phantom limb pain. We conclude, that different parts of the motor system are affected in patients with phantom limb pain – possibly in the sense of an up-regulation of excitability. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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Cortical reorganization is an intriguing topic in patients with upper extremity amputation. It has been suggested that cortical reorganization might be an important cause of phantom limb pain [1,4]. Although phantom limb pain represents a primary sensory phenomenon, some patients also report on the experience of active or passive limb movements with the phantom limb. Purposeful re-use of the amputated limb by a functional prosthesis has been demonstrated to decrease the intensity of phantom limb pain [9]. These observations suggest that reorganization in the motor network is also of importance for the occurrence and maintenance of phantom limb pain. The aim of the present study was to investigate whether the motor system shows alterations of cortical orga-

nization in addition to reorganization in the sensory system. We also wanted to determine whether reorganization is restricted to the hemisphere contralateral to amputation, and whether it is associated with phantom limb pain.

Sixteen patients were investigated (two females, 14 males, all right-handed according to the Edinburgh questionnaire) with upper limb amputation (Table 1). Average age at the time of investigation was 38 years (13–69). Average age at the time of amputation was 26 years (1–69). Four patients suffered amputation of the forearm. Twelve had upper arm amputation. Six amputations were located on the left, ten on the right side. In fourteen patients the underlying cause was an accident. Two suffered from complications and malignant tumours (Ewing sarcoma, histiocytoma). All patients were familiar with phantom sensations. Five confirmed the existence of rare telescoping. Eight patients denied ever having experienced phantom

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Table 1  
Clinical characteristics of 16 patients with upper limb amputation

Patient	Age at study	Amputation age	Location	Side	Course	Phantom sensation	Telescoping	Phantom pain	Shift of representation	Increased activation
1	48	48	Lower arm	Right	Traumatic amputation	Yes	Discreet	Yes	Yes	Yes
2	33	31	Upper arm	Right	Infection of elbow prosthesis	Yes	Yes	Yes	No	No
3	29	18	Upper arm	Right	Accident	Yes	Yes	Yes	Yes	Yes
4	44	31	Upper arm	Right	Traumatic destruction	Yes	Yes	Yes	No	Yes
5	49	31	Upper arm	Right	Accident	Yes	Yes	Yes	No	Yes
6	59	59	Upper arm	Left	Traumatic destruction	Yes	Discreet	Yes	Yes	Yes
7	69	69	Upper arm	Left	Pathological fracture	Yes	Discreet	Yes	No	No
8	58	23	Upper arm	Left	Chronic osteomyelitis	Yes	Yes	Yes	No	No
9	37	37	Upper arm	Right	Polytrauma	Yes	Discreet	No	No	Yes
10	13	11	Upper arm	Right	Traumatic amputation	Yes	Yes	No	No	No
11	29	8	Lower arm	Right	Traumatic amputation	Yes	Yes	No	No	Yes
12	25	16	Lower arm	Right	Traumatic destruction	Yes	Yes	No	No	No
13	44	13	Lower arm	Right	Traumatic destruction	Yes	Yes	No	Yes	Yes
14	16	15	Upper arm	Left	Power current accident	Yes	Discreet	No	Yes	Yes
15	22	7	Upper arm	Left	Traumatic nerve/vessel destr.	Yes	Yes	No	Yes	Yes
16	39	1	Upper arm	Left	Traumatic destruction	Yes	Yes	No	Yes	Yes

limb pain. Eight confirmed occasional phantom limb pain (Table 1). All patients were able to differentiate between stump and phantom limb pain. At the time of the investigation no patient complained of pain.

A group of six, right-handed healthy volunteers (average age 29, four males, two females) served as control. All volunteers and patients signed an informed consent. The study was in agreement with the Declaration of Helsinki.

A functional magnetic resonance imaging study was performed using single slice FLASH technique and a Philips Gyroscan ACS II (TR/TE/alpha 100/50/40)[2]. Measurements were performed in a transverse section between 45 and 55 mm dorsal and parallel to the anterior and posterior commissure. The precise plane was identified by the characteristic shape of the central sulcus of the unaffected hemisphere [10]. Slice thickness was 10 mm. One hundred measurements were executed during five different conditions: rest (A); tapping with the index finger and thumb of the intact hand (B); anteflexion of the intact arm (C); anteflexion of the amputation stump (D); and repetitive eye closure (E). Prior to scanning volunteers and patients were carefully instructed and practiced to perform the movements at a rate of about one Hz. Care was given that rate and amplitude of the intact shoulder and stump movement or right and left shoulder were similar. The philosophy of choosing this particular plane was that it contains the cortical hand representation and that it is located between the shoulder representation and the face representation. Increased activation during face or shoulder movement would suggest invasion of the neighbouring representations into the cortical hand representation. Data from six patients with left-sided amputation were mirrored at a sagittal plane for group analysis, as if all patients had an amputation on the left side. Data were analysed using SPM96 applying a motion correction, a filter kernel of 3 mm for single subject analysis and 6 mm for group analysis, and an ANCOVA [5].

Individual and group results are reported at  $P < 0.001$ . Data were normalized on a standard template in this particular plane for between-group comparison. Group results are displayed as projection on an individual normalized plane.

Finger tapping induced an activation in the contralateral sensorimotor cortex (SMC) in all volunteers. Activation was located in all volunteers within the 'knob' of the central sulcus. In two volunteers repetitive eye closure caused a small bilateral activation in the very lateral part of the central sulcus, and one volunteer showed a unilateral activation. Anteflexion of the right and left shoulder produced a contralateral activation in four out of six cases. Activation during shoulder anteflexion was located mesial to the knob.

Finger tapping produced a 'normal' activation in the contralateral SMC in twelve patients. Three patients presented a large activation in the contralateral SMC. Two of these as well as another one showed a bilateral activation of the SMC. Twelve patients showed some activation in SMC during repetitive eye closure, predominantly in the lateral part of the central sulcus. Five patients showed a bilateral activation. Anteflexion of the intact arm caused several activation patterns. Activation was more frequent in patients than in normal volunteers. Fifteen of sixteen patients showed some activation in this particular transverse plane during shoulder anteflexion. The activation was extensive in nine patients during shoulder movements on either side. In three patients activation was contralateral during anteflexion of the amputation stump, ipsilateral in one patient and bilateral in another. Five patients showed an activation in the contralateral SMC during anteflexion of the intact arm. One patient showed an activation ipsilateral to the movement and another contralateral to amputation. The activated focus was located more mesial to the 'Omega' of the central sulcus in five patients.

Group analysis of all sixteen patients revealed an activation in the contralateral SMC and supplementary motor area

(SMA) during finger tapping and a weak activation during repetitive eye closure. A strong activation in the mesial part of the SMC and SMA was bilaterally generated during ante-flexion of the amputation stump. A strong activation was induced in the contralateral SMC and SMA during ante-flexion of the intact shoulder.

Patients were divided into two groups: those who had experienced phantom limb pain and those unfamiliar with phantom limb pain. Patients with phantom limb pain showed a very broad, extensive, bilateral activation in the SMC and SMA during ante-flexion of the amputation stump (Fig. 1, left panel). Patients without phantom limb pain presented activation restricted to the mesial part of the SMC contralateral to the amputation (Fig. 1, right panel). Activation in the SMA during ante-flexion of the intact shoulder was more likely in those patients with phantom limb pain (Fig. 2, left panel) than in those without pain (Fig. 2, right panel).

A between-group comparison in patients with phantom limb pain and those without confirmed an increased likelihood of activation in SMA ipsilateral to the stump during ante-flexion of the stump (Fig. 3, left panel). Activation in the contralateral SMC and ipsilateral SMA was more likely during ante-flexion of the intact arm (Fig. 3, right panel). The opposite contrast (patients without experience of phantom limb pain versus those with experience) revealed no significant activation.

The present results contain several important clues regarding the organization of the motor system and the generation of phantom limb pain:

The present data suggest that the central sulcus within this

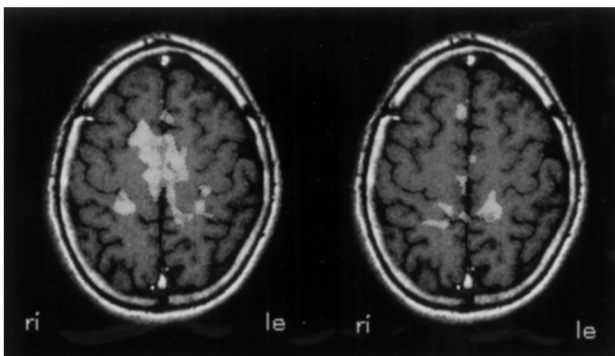


Fig. 1. Categorical comparison between movement of the amputation stump and rest for patients with experience of phantom limb pain (left panel) and without pain experience (right panel). Significant activations ( $P < 0.001$ ) are displayed in white and projected on the T1 weighted MRI image of a normalized individual. Left hemisphere (le) is displayed on the right side in radiological convention. Ante-flexion of the amputation stump in patients with phantom limb pain (left panel) reveals an activation of the contralateral shoulder representation within the primary sensorimotor cortex (mesial to the hand representation within the 'inverted Omega') and a bilateral activation of the SMA. This activation is much stronger in patients with phantom limb pain than in those patients without phantom limb pain (right panel).  $P < 0.001$ .

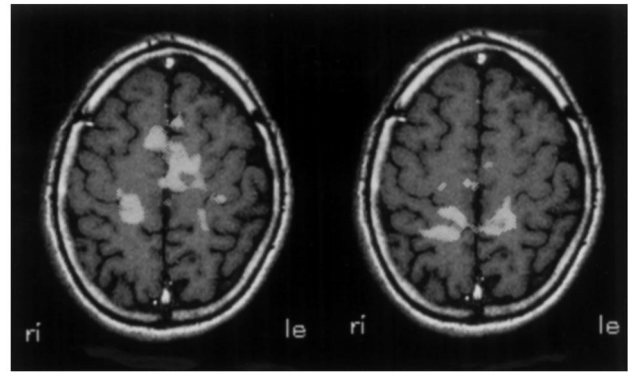


Fig. 2. Categorical group comparison between movement of the intact shoulder in patients with the experience of phantom limb pain and rest (left panel) and in patients without experience of phantom limb pain (right panel). Ante-flexion of the intact shoulder in patients with phantom limb pain (left panel) causes an activation of the mesial part of the contralateral SMC and the bilateral SMA. It causes an activation of the bilateral mesial part of the SMC in patients without phantom limb pain (right panel).  $P < 0.001$ .

particular transverse plane contains a specific topographical organization: The face is represented in the very lateral part of the central sulcus. The hand is represented in the middle, within the 'knob' of the sulcus. The shoulder is located on its mesial side. This suggests the existence of a 'partial homunculus' within each transverse plane. We do not suggest that this topographical organization is strict or rigid. We assume that the functional organization, i.e. differ-

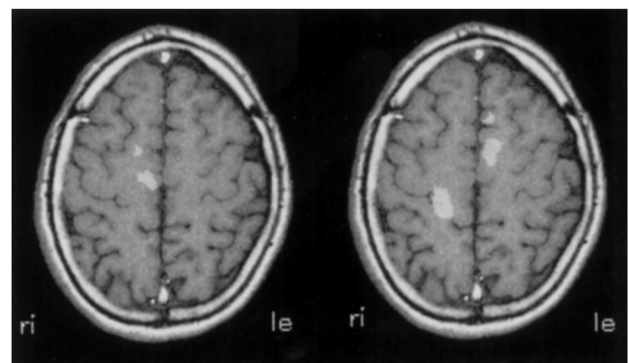


Fig. 3. Between-group comparison of activation in patients with and without phantom limb pain for movements of the amputation stump (left panel) and the intact shoulder (right panel): Ante-flexion of the amputation stump causes a significant ( $P < 0.001$ ) higher activation of the SMA ipsilateral to the stump in patients with phantom limb pain compared to those without experience of pain (left panel). Ante-flexion of the intact shoulder caused a higher activation in the contralateral SMC and ipsilateral SMA in patients with phantom limb pain compared to those with no experience of phantom limb pain (right panel). Please note: patients had no pain at the time of the investigation. The figure illustrates that the motor cortex of patients with the experience of phantom limb pain has a higher excitability than the motor cortex in patients without phantom limb pain experience. The reverse comparison (patients without phantom limb pain versus patients with pain) did not indicate any significant activation.

ent neural assemblies representing the function of grasping, pinch grip etc., may still be dominant [7,8].

The motor system is affected in both hemispheres. There is a shift of cortical representation into neighbouring areas. There exists increased likelihood of activation in the hemisphere contralateral to the amputation stump. It has been suggested that this activation reflects intracortical disinhibition. Furthermore, a similar increased activation was observed in the hemisphere ipsilateral to amputation. This may be explained by the lack of transcallosal or transhemispheric inhibition. It confirms the close interaction between both hemispheres [3,6]. A lesion or even a malfunction in one hemisphere is likely to cause a malfunction in the opposite hemisphere.

Of particular interest is the increased activation of the SMA in patients with phantom limb pain. There is a systematic difference in age at amputation and age at scanning between both groups. This cannot be corrected for and is in line with previous observations, that amputation at an early age is less likely to produce phantom pain. Previous investigations focused on the shift of cortical representations into neighbouring areas particularly in the primary motor cortex, primary somatosensory cortex and parietal cortex [1,4]. The present data confirm this shift of representations within the motor cortex. Increased activation of SMA, however, contains additional information and indicates that large parts of the motor system show increased activity, probably due to an increase of excitability after amputation of a limb. Increased excitability of the primary motor cortex was recently confirmed by single case studies using transcranial magnetic stimulation [6]. Increased activation of SMA suggests that the motor system, in general, is affected in patients with phantom limb pain. It is not clear, whether increased excitability is the cause or consequence of phantom limb pain. Its existence confirms the role of the motor system in the information process of pain. Our results parallel recent observations that patients wearing a functional prosthesis rarely experience phantom limb pain [9]. It also underpins the value of physiotherapy or motor exercise in the treatment and prevention of phantom limb pain.

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