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Illusory movements of the paralyzed limb restore motor cortex activity

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Abstract

In humans, limb amputation or brachial plexus avulsion (BPA) often results in phantom pain sensation. Actively observing movements made by a substitute of the injured limb can reduce phantom pain (V.S. Ramachandran and D. Rogers-Ramachandran, 1996, Proc. R. Soc. London B Biol. Sci. 263, 377–386). The neural basis of phantom limb sensation and its amelioration remains unclear. Here, we studied the effects of visuomotor training on motor cortex (M1) activity in three patients with BPA. Functional magnetic resonance imaging scans were obtained before and after an 8-week training program during which patients learned to match voluntary "movements" of the phantom limb with prerecorded movements of a virtual hand. Before training, phantom limb movements activated the contralateral premotor cortex. After training, two subjects showed increased activity in the contralateral primary motor area. This change was paralleled by a significant reduction in phantom pain. The third subject showed no increase in motor cortex activity and no improvement in phantom pain. We suggest that successful visuomotor training restores a coherent body image in the M1 region and, as a result, directly affects the experience of phantom pain sensation. Artificial visual feedback on the movements of the phantom limb may thus "fool" the brain and reestablish the original hand/arm cortical representation.

Keywords: Motor cortex; Motor plasticity; Brachial plexus avulsion; Illusory movements; fMRI

Introduction

Subjects with amputation of the upper limb often report vivid pain sensation and illusion of movement of the missing arm (Kooijman et al., 2000). Similar experiences are reported by patients suffering from brachial plexus avulsion (BPA) resulting in limb paralysis and deprivation of somatosensory input (Parry, 1980). These phenomena have been interpreted as reflecting a reorganization of the deafferented hand representation and the adjacent body segments in motor regions of the cerebral cortex (Cohen et al., 1991; Flor et al., 1995). Interestingly, it has been claimed that artificial visual feedback of the lost or paralyzed limb, obtained through a transposition of the intact arm's movements onto the affected side, can attenuate painful sensation (Ramachandran and Rogers-Ramachandran, 1996). This raises the question whether changes in the subjective experience of the phantom limb result from changes in the activity of specific cortical regions. Recent results suggest that the motor cortex may be an important site of cortical plasticity. Both humans and nonhuman primates show extensive reorganization of the hand region after peripheral injury of the upper limb, with the representation of the adjacent body part "invading" the cortical territory previously occupied by the hand (Cohen et al., 1991; Flor et al., 1995; Wu and Kaas, 1999). Interestingly, the extent of cortical reorganization is correlated with the degree of phantom pain sensation (Flor et al., 1995), and this reorganization can be reversed by hand transplant (Giraux et al., 2001). Although the link between M1 activity and pain sensation is not clearly established, electrical stimulation of M1 in neurological patients with chronic pain has strong analgesic effects (Garcia-Larrea et al., 1999). In this study, we test the hypothesis whether exposure to virtual limb movements induces plastic changes in the cortical representation of the impaired limb and whether this plasticity is correlated with changes in phantom pain sensation.

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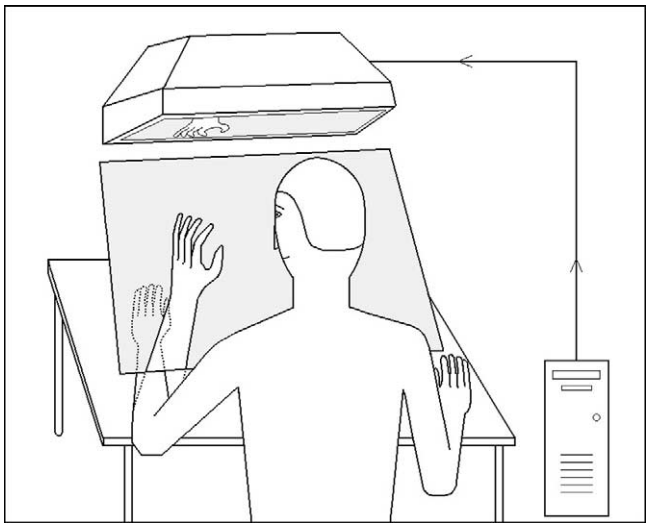

Fig. 1. The experimental training setup (see Materials and methods).

Materials and methods

Three patients, CH, DU, and RA, suffering from a traumatic brachial plexus avulsion were included in this study, which was approved by the local ethics committee. Subject CH is a 41-year-old right-handed man who sustained a left BPA in 1999 extending from cervical root C5 to C8, followed by a complete left upper limb paralysis and anesthesia associated with vivid and painful phantom limb. The phantom pain was perceived as burning and clenching of the whole hand radiating toward the elbow. Despite drug therapy (gabapentin, clonazepam, morphine) the mean level of pain was quoted at 7 on the Visual Analogue Scale (Price et al., 1983). Patient DU is an 18-year-old right-handed male with a complete right BPA that occurred in June 2000. Pain characteristics in this subject were similar to those of CH, with the exception that the phantom pain was experienced as a constriction of the wrist and a cramp of the hand. Drug therapy consisted of carbamazepine and clonazepam. Subject RA is a 40-year-old right-handed man who had a right BPA in 1998 that affected spinal root C6 to D1. Phantom pain was perceived as electric discharges of the hand and elbow. Drug therapy included gabapentin, clonazepam, and morphine. It is important to note that the patients were under drug treatment throughout the whole study.

Subjects were exposed to virtual movements of their impaired limbs through a video-optical system (Fig. 1). The basic procedure was inspired by the study of Ramachandran and Rogers-Ramachandran (1996). The training equipment consisted of a PC computer (Matrox Millenium video card), a video camera, an 18-in. LCD screen, and two mirrors. During training subjects sat in front of a table and placed the impaired limb below a 45°-oriented mirror and the intact arm on the table. A video monitor placed above the mirror projected the image of hand movements onto the mirror. Subjects perceived those hand movements at a location coinciding with their impaired hand. The visualized hand movements were prerecorded movements of the intact hand (640×480 pixels, 25 images s^{-1}) obtained prior to training. A variety of movements were included at slow, normal, and fast speeds (opening/closing the hand, fingers-to-thumb opposition sequence, grasping various types of object) and stored in the PC. The prerecorded movements were projected (using a specially designed software) on the paralyzed side to give subjects the illusion that the impaired hand was moving. Subjects were asked to produce a hand movement with their phantom limb while watching the hand in the mirror. Sessions started with simple and slow movements, then the speed and complexity gradually increased dependent on the subject's report of his kinesthetic and pain sensations. Each subject completed 24 sessions, at a rate of 3 sessions per week, each session involving 100 movements. In patients with phantom pain, voluntary movement of the phantom limb is painful by itself. Thus, pain level was assessed before and after each session in two ways: first, subjects reported a percentage of pain relief ranging from 0 (no relief) to 100 (complete relief). Second, they marked on a 100-mm Visual Analogue Scale the average pain level (Price et al., 1983).

The effects of visuomotor training on cortical motor activity were assessed by comparing two identical fMRI exams, the first before training and the second at the end of the program. Four conditions of movement were tested in four independent runs following a constant order: 1—opening/closing the hand, normal side; 2—flexion/extension of the elbow, normal side; 3—opening/closing the hand, affected side; 4—flexion/extension of the elbow, affected side. For the paralyzed side, subjects were explicitly asked to "perform the movement with their phantom limb." These movements were chosen because all subjects could perform them with their phantom limb. Data were acquired on a clinical MRI machine (1 T, Magnetom Impact, Siemens, EPI sequences, 3.5×3.5 in-plane resolution, 6-mm thickness, 18 slices per scan, covering entirely both cerebral hemispheres, repetition time 5 s). A block of fMRI design was applied with regularly spaced short epochs of the movement condition (15 s, 3 scans, 9 blocks per run) alternating with longer epochs of rest (25 s, 5 scans, 10 blocks per run), with a total of 80 scans per run (the first 3 scans being discarded from further analysis). For each movement epoch, an auditory "go" signal informed the subject to start moving, then movements were rhythmically repeated until a second auditory "stop" signal informed the subject to stop moving. Frequency of movement was self-paced and individually defined prior the fMRI exams, based on the time of speed of movement of the phantom limb, and then applied to the normal side. To ensure that movement rhythm remained constant, movements of the intact hand were visually monitored during the scans, while a postexamination movement speed retest was done of the affected side. Statistical analyses were performed with SPM99 (Wellcome Department of Cognitive Neuroscience, UK) and Matlab

Table 1
Effect of visuomotor training on M1 activation and on mean pain level

Subject	M1 activation[a]										
	Hand				Elbow				Pain[b]		
	Z score		Cluster size		*Z* score		Cluster size		VAS		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	% Relief
DU	5	11	1	104	7	12	46	348	7	1.5	80
CH	7	14	9	317	6	12	12	392	7	4	40
RA	0	0	0	0	0	5	0	49	7	6	0

[a] Maximal *Z* score and cluster size in voxel.
[b] Pain evaluation as assessed by the Visual Analogue Scale (VAS) and the percentage relief scale.

6.1 (Mathworks, Inc., USA) on a personal computer (Windows 2000). Preprocessing of the MR images included slice-timing correction, realignment, coregistration on the individual T1-weighted MRI ($2 \times 2 \times 2$-mm resolution), and spatial smoothing (Gaussian filter, FWHM 7 mm). For each subject, MRI time series was modeled with a boxcar model convolved with a standard hemodynamic response flow. For each individual condition, a *t* test was performed on the residual variance of the model and transformed into a *Z* score 3-D map. Results were considered significant at $p < 0.05$ (intensity threshold corrected for spatial extent). To separate M1 activity from S1 and premotor activity, the individual 3-D shape of the central sulcus was extracted from the anatomical T1-weighted MRI. Voxels were considered as belonging to M1 if they were located in front of the central sulcus and within a 6-mm distance.

Results and discussion

Patients CH and DU showed similar patterns of cerebral activation. As expected, finger and elbow movements of the normal limb activated the contralateral primary sensory and motor cortices. The distribution and intensity of these activations remained stable across the pre- and posttraining scans. Pretraining finger and elbow movements by the phantom of the paralyzed limb induced a weak activation in the contralateral motor regions, mainly located in the caudal part of the dorsal premotor cortex (PMd), marginally extending into M1 (Table 1 and Fig. 2). Posttraining, premotor cortex activity increased significantly compared to the pretraining exam. More importantly, a dramatic change was observed within the M1 hand and arm representations, in terms of both activation level and size (number of voxels) of the activated region (Table 1 and Fig. 2). By contrast, subject RA showed no such change. Before training, cerebral activation for movements of the phantom limb were confined to the rostral part of PMd. After training, M1 activity was not enhanced during finger movements of the phantom limb and only weakly increased during elbow movements (Table 1 and Fig. 2). Surprisingly, increases in M1 activity were observed in the second exam during movements of the normal limb for this subject (Z_{max} hand, from 16 to 28; elbow, from 9 to 24). The line plots in Fig. 2 summarize the results for the three patients by showing the ratio of M1 activation between the impaired and the normal limb. Behaviorally, the increased activity in motor areas in subjects DU and CH was accompanied by a reduction in the self-reported intensity of phantom pain (Table 1). By contrast, subject RA's pain assessments showed no noticeable changes. Pain assessments had consequences for the subjects' pain control therapy: at the end of the training program, CH quit using morphine, and DU stopped all drugs. This effect was still observed 6 months later. In contrast, RA maintained his pretraining drug regimen.

These results show that the primary motor cortex can undergo extensive changes even as a result of training purely phantom limb movements, which are nevertheless experienced as real by these subjects. What are the mechanisms of this cortical plasticity? A possible explanation is that movements of the paralyzed limb's phantom restore a coherent body image representation that was lost after the injury. Following peripheral injuries, motor commands can still be issued by the intact sensorimotor structures and are probably at the origin of the phantom sensations, directly or through internal "copies" of these motor commands fed back to other cortical areas such as the parietal and premotor cortices. However, since efferent motor signals produce no movement, and hence no proprioceptive input, a mismatch must occur between the normally correlated efferent and reafferent information, yielding an error signal (see also Blakemore et al., 2002). We hypothesize that over time, this may result in weakened motor outflow and temporarily erase limb movement representations in M1. However, under certain conditions, motor activity can be reawakened and increase phantom movement experiences, either spontaneously or as a result of some external trigger, such as viewing images of limb movements. This may be related to activity in the so-called mirror neuron system first described in the premotor cortex of nonhuman primates in which the mere observation of an action is sufficient to evoke neuronal responses (Rizzolatti and Luppino, 2001). Imaging studies in humans have also shown that action observation facilitates activity in a network of parietofrontal structure in-

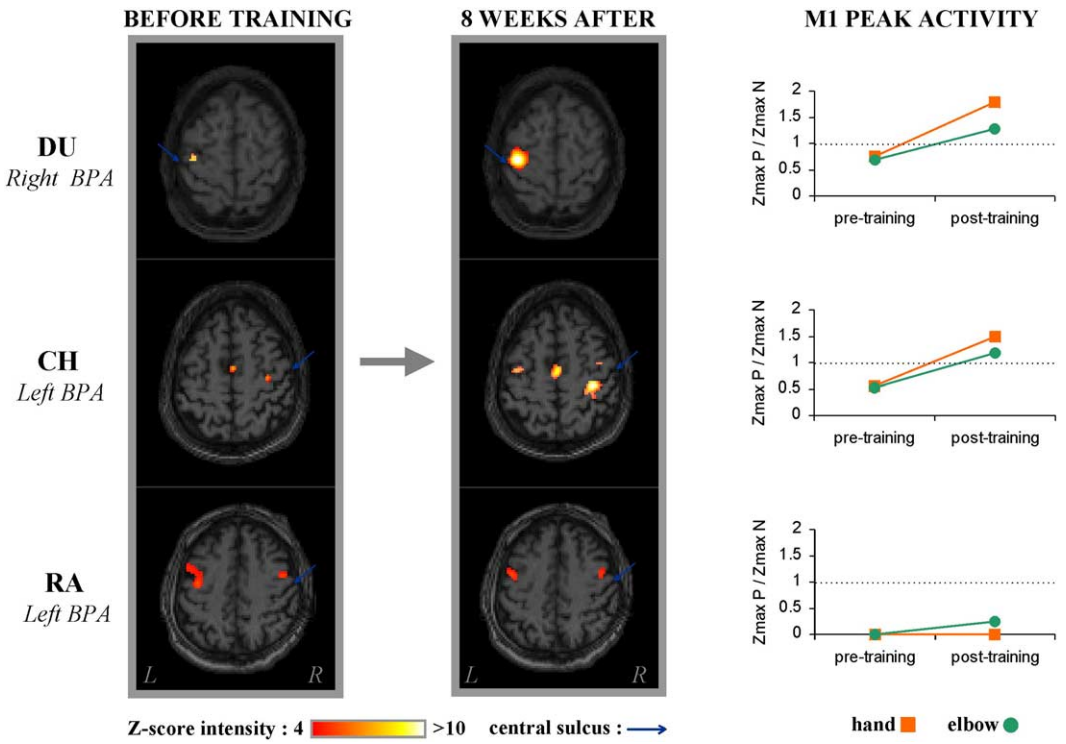

Fig. 2. Individual significant activations in motor regions (superimposed on individual anatomical MRI) for phantom hand "movements" before training (left) and after training (middle). The plots on the right illustrate the evolution of M1 activations (Z_{max}) by showing the ratio of maximal activity for the phantom limb (P) compared to the normal limb (N).

volved in motor planning (Buccino et al., 2001; Grafton et al., 2001). Interestingly, we observed that even before the visuomotor training program began, passively exposing the subjects to the prerecorded movement of the hand in the experimental setup induced strong (and sometimes painful) phantom experiences. Furthermore, the pretraining fMRI scans showed that activity during voluntary movements of the phantom limb was primarily located in the premotor areas, where mirror neurons are found. During training, providing the motor system with a model of the limb movement via the parietopremotor gateway introduces novel correlations between inflow and outflow signals. We argue that this process contributes to restoring coherence in the upper limb representation in M1 and that the expansion of the fMRI signal in M1 after training is the expression of a reactivated motor image of the upper limb which, through learning, becomes more automatically accessed. The reason for failure of the visuomotor training to induce cortical changes in subject RA is unclear. One possibility is the time elapsed since injury (6months for DU, 2 years for CH, 5 years for RA). There might therefore be a critical window of opportunity to trigger plasticity of motor cortex via visual feedback.

Our results indicate that a close link exists between restoration of M1 activity and phantom pain reduction. What is the nature of this link? Early hypotheses about the genesis of this chronic pain implicated neural reorganization in the spinal (Devor and Wall, 1978) and thalamic sensory relays (Garraghty and Kaas, 1991). Recently, a more direct relation between M1 and pain has been hypothesized. As mentioned above phantom pain severity in amputees increases with the shrinkage of the limb representation in M1 (Flor et al., 1995) and chronic electrical stimulation of motor cortex in neurological patients attenuates pain (Garcia-Larrea et al., 1999). Interestingly, the subjects in the present study reported that pain increased when the displayed movement exceeded the ability of their phantom limb to match it (e.g., if the movements were too fast), while pain decreased in the case of an adequate match. Although there is no clear explanation at this time of the way in which brain areas involved in processing movement interact with those monitoring pain, such as somatosensory cortex (Peyron et al., 2000), our results and those from the literature suggest that some form of inhibitory control might be exerted by motor cortex. Finally, from a therapeutic point of view our results suggest that a wide range of pathological conditions could benefit from this visuomotor technique, for the purpose of either pain relief (e.g., neuropathic pain, reflex sympathetic dystrophy) or motor rehabilitation (e.g., stroke, nerve lesions, orthopedic immobilization).

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References

Blakemore, S.J., Wolpert, D.M., Frith, C.D., 2002. Abnormalities in the awareness of action. Trends Cognit. Sci. 6, 237–242.

Buccino, G., Binkofski, F., Fink, G.R., Fadiga, L., Fogassi, L., Gallese, V., Seitz, R.J., Zilles, K., Rizzolatti, G., Freund, H.J., 2001. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur. J. Neurosci. 13, 400–404.

Cohen, L.G., Bandinelli, S., Findley, T.W., Hallett, M., 1991. Motor reorganization after upper limb amputation in man: a study with focal magnetic stimulation. Brain 114, 615–627.

Devor, M., Wall, P.D., 1978. Reorganization of spinal cord sensory map after peripheral nerve injury. Nature 276, 75–76.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., Larbig, W., Taub, E., 1995. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 375, 482–484.

Garcia-Larrea, L., Peyron, R., Mertens, P., Gregoire, M.C., Lavenne, F., Le Bars, D., Convers, P., Mauguiere, F., Sindou, M., Laurent, B., 1999. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83, 259–273.

Garraghty, P.E., Kaas, J.H., 1991. Functional reorganization in monkey thalamus after peripheral nerve injury. NeuroReport 2, 747–750.

Giraux, P., Sirigu, A., Schneider, F., Dubernard, J.M., 2001. Cortical reorganization in motor cortex after graft of both hands. Nat. Neurosci. 4, 691–692.

Grafton, S.T., Salidis, J., Willingham, D.B., 2001. Motor learning of compatible and incompatible visuomotor maps. J. Cognit. Neurosci. 13, 217–231.

Kooijman, C.M., Dijkstra, P.U., Geertzen, J.H.B., Elzing, A., Van der Schans, C.P., 2000. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. Pain 87, 33–41.

Parry, C.B., 1980. Pain in avulsion lesions of the brachial plexus. Pain 9, 41–53.

Peyron, R., Laurent, B., Garcia-Larrea, L., 2000. Functional imaging of brain responses to pain: a review and meta-analysis. Neurophysiol. Clin. 30, 263–288.

Price, D.D., McGrath, P.A., Rafii, A., Buckingham, B., 1983. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 17, 45–56.

Ramachandran, V.S., Rogers-Ramachandran, D., 1996. Synaesthesia in phantom limbs induced with mirrors. Proc. R. Soc. London B Biol. Sci. 263, 377–386.

Rizzolatti, G., Luppino, G., 2001. The cortical motor system. Neuron 31, 889–901.

Wu, C.W., Kaas, J.H., 1999. Reorganization in primary motor cortex of primates with long-standing therapeutic amputations. J. Neurosci. 19, 7679–7697.