CORTICAL MOTOR ACTIVATION PATTERNS FOLLOWING HAND TRANSPLANTATION AND REPLANTATION

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We studied cortical activation patterns by functional MRI in a patient who received bilateral hand transplantation after amputation 6 years ago and in a patient who had received unilateral hand replantation within 2 hours after amputation. In the early postoperative period, the patient who had had the hand transplantation revealed strong activation of a higher motor area, only weak activation of the primary sensorimotor motor cortex and no activation of the primary somatosensory cortex. At 1-year follow-up, a small increase in primary sensorimotor motor cortex activation was observed. Activation of the primary somatosensory cortex was only seen at the 2 year follow-up. By contrast, after hand replantation, the activation pattern was similar to that of the uninjured hand within 6 weeks. This included activation of the primary sensorimotor motor cortex, higher motor areas and primary somatosensory cortex. Transplantation after long-standing amputation results in cortical reorganization occurring over a 2-year period. In contrast, hand replantation within a few hours preserves a normal activation pattern.
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INTRODUCTION

Cortical reorganization after limb deafferentation is a well-known phenomenon which includes a decrease of cortical representation in the motor and sensory areas. In primates, an increased representation in the adjacent cortical areas has been observed (Qi et al., 2000). Similarly, an enlargement of stump and shoulder cortical representation was found in human limb amputees (Cohen et al., 1991; Dettmers et al., 1999; Fuhr et al., 1992; Kew et al., 1994; Pascual-Leone et al., 1996). However, little is known as to whether this reorganization is reversible by hand transplantation several years after the primary injury. One study suggested that cortical reorganization is quickly reversible after bilateral hand transplantation (Giraux et al., 2001).

To investigate the time course of cortical reorganization after hand transplantation, we determined the activation pattern of simple finger movements in a patient who received bilateral allogenic hand transplantation after amputation 6 years previously. For comparison, cortical activation was studied 6 weeks as well as 12 and 24 months after surgery in a patient who underwent an autologuous hand replantation 2 hours after amputation.

PATIENTS AND METHODS

Patients

(1) A 47 year-old, right-handed male who received two allograft hand transplants 6 years after amputation at wrist level in a bomb injury (Piza-Katzer et al., 2002).
(2) A 20 year-old, right-handed female who lost her left hand at wrist level in a saw injury and who underwent replantation 2 hours after the accident.

Both patients were included in an intensive rehabilitation program.

Methods

These patients were investigated by functional MRI 6 weeks, 12 and 24 months postoperatively. Clinical examinations were performed before acquisition of MR images. Both subjects gave their informed consent to the study. Subjects were scanned with the head immobilized and eyes closed. Both arms rested comfortably to prevent activity of the proximal arm muscles. Subjects were instructed to perform a flexion/extension movement of all the fingers of each hand at 0.5 to 1 Hz. All tasks were under continuous visual control of one of the investigators.

Data were acquired with a 1.5 T MR Scanner (Magnetom Vision, Siemens, Erlangen, Germany). EPI sequences were used to obtain functional images in parallel orientation to ACPC line with a TE of 64 ms, slice thickness 3 mm, interslice gap 0.3 mm, matrix of 128×64, and a field of view (FoV) of 220 mm.The images covered the whole brain except the posterior lobe of the cerebellum. All active conditions were repeated 6 times in a pseudo-random order, each repetition contained five brain volumes. Acquisition time of the brain volume lasted 5.5 s with 1.5 s interval time between two scans. Between the conditions, the subjects were acoustically instructed of the next condition. For anatomical overlay the image protocol comprised a sagittal T1-weighted FLASH 3D with a repetition time (TR) of 9.7 ms, echotime (TE) 4 ms, slice thickness 1.23 mm, matrix of 256 × 256, and a FoV of 230 mm. Data were processed using statistical parametric mapping (SPM99, The Wellcome Department of Cognitive Neurology, London, UK). Within each individual fMRI session, all scans were realigned on the first scan and subsequently co-registered to the anatomical images and transformed into standard stereotactical space (Talairach and Tournoux, 1988). After smoothing with a Gaussian kernel filter of 3 mm FWHM in x, y, z axes to increase signal-to-noise ratio, a design matrix with contrasts of interest and confounding effects (high pass filter of 160 s) was established. The general linear model was used to assess voxel based t-statistic. A significance level of $P<0.01$, corrected for multiple comparison (small volume correction $r = 15$ mm), was applied.

RESULTS

1. Hand Transplantation Patient

Six weeks after surgery, the patient showed finger flexion and extension of grade 3, according to the British Medical Research Council Scale (MRC Grade 3, active movement against gravity; Grade 4, active movement against resistance and gravity; Grade 5, normal power) in both hands. He was unable to oppose the thumb to the little finger. At 1 year, finger flexion and extension improved markedly to grade 4 MRC without any improvement in intrinsic hand muscle weakness. Surface and deep sensation improved partially. The patient was able to identify light touch, painful pin prick stimuli and several finger positions. At 2 years, strength had improved further to MRC 4-5 for flexion and extension.

During left hand movement, baseline fMRI revealed activation in the contralateral supplementary motor area (SMA), while only weak activation was seen in the right sensorimotor motor cortex (SM1) (see Fig 1). At 1 year, activation in the right SM1 was similar to that in the early postoperative period but the primary somatosensory area (SS1) was still not activated. Two years after transplantation, an increase of SM1 activation and activation of the right SS1 were observed (see Fig 1). For a summary of location and Talairach coordinates of peak maxima see Table 1. Similar activation patterns were observed during movements of the transplanted right hand.

2. Hand Replantation Patient

Clinical evaluation, 6 weeks after left hand replantation, revealed finger flexion and extension weakness grade 3 MRC and complete weakness of the intrinsic hand muscles. After 1 year, finger flexion and extension improved to grade 4 MRC without a change in the palsy of the small hand muscles. As with patient 1, flexion and extension strength had improved further to MRC grade 4–5 by 2 years after replantation.

Six weeks after surgery, cortical activation comprised the contralateral SM1, the SMA proper, SS1 and premotor cortex and was strikingly similar to the cortical activation pattern during movements of the right uninjured hand. During the 1- and 2-year follow-up studies, this activation pattern remained unchanged (Table 2).

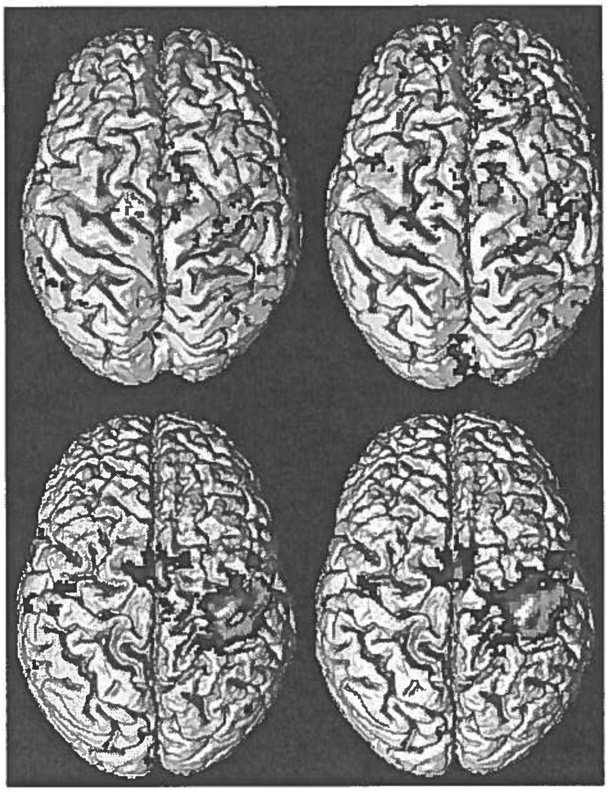

Fig 1 Activation pattern of left finger flexion and extension after hand transplantation (upper row) and replantation (lower row); investigation 6 weeks (left) and 2 years postoperative (right).

Table 1—Cortical activation pattern in bilateral hand transplantation, flexion and extension of left fingers; investigation 6 weeks and 2 years postoperative

Anatomical location		*6 weeks*			*2 years*		
	BA	*x*	*y*	*z*	*X*	*y*	*z*
SM1 right	4	38	−30	66	30	−36	70
SMA proper right	6	9	−9	54	4	−16	54
SS1 right					48	−33	62

BA, Brodmann's area; SM1, primary sensorimotor cortex; SMA, supplementary motor area.

Table 2—Cortical activation pattern in left hand replantation, flexion and extension of left fingers; investigation 6 weeks and 2 years postoperative

Anatomical location	*6 weeks*				*2 years*		
	BA	*x*	*y*	*z*	*X*	*y*	*z*
SM1 right	4	35	−29	66	35	−29	66
SMA proper right	6	3	−3	50	2	−6	56
PM right	6	44	−12	62	36	−15	68
SS1 right	5	42	−36	66	38	−38	69

BA, Brodmann's area; SM1, primary sensorimotor cortex; SMA, supplementary motor cortex; PM, premotor cortex.

DISCUSSION

Functional MRI allows us to investigate cortical activation during various tasks. In healthy controls, simple finger movements lead to activation of the primary sensomotor (SM1) and somatosensory (SS1) cortex as well as in the higher motor areas. The main higher motor region is the supplementary motor area (SMA), which is located in the mesial wall of the frontal cortex. This region is known to participate on programming motor plans. Additional function in preparing movements is based in the lateral premotor cortex, which is close to the primary motor cortex in the frontal lobe. In complex motor tasks, activation is also observed in the parietal cortex which provides proprioceptive and visual informations for the movement planning and control.

In this study, we determined the cortical activation pattern during a simple motor task after short (2 hours) and long-term (6 years) deafferentation. The clinical motor recovery of our patients was comparable, whereas functional imaging revealed different cortical activation patterns. Six weeks postoperatively, the activation pattern in the patient who had had long-standing amputation contained activation of the SMA proper and only a small cluster of activity in SM1, whereas a virtually normal activation pattern was found after allogenic hand replantation, with a short period of deafferentation, including that in the primary and higher motor areas, as well as in the SS1. SMA activation appears to be more resistant to the consequences of amputation. This finding might be related to the SMA function of motor programming (Tanji, 1996) which can be trained by motor imaging or the use of myo-protheses. Furthermore, evidence exists from anatomical studies that direct connections exist from the SMA to the spinal cord (Dum and Strick, 1996). This pathway could compensate for lost projections from the primary motor cortex after long-term amputation and would be in keeping with the clinical observation that motor recovery of our two patients was similar.

The activation pattern 6 weeks after hand replantation was not different from that seen during movements of the uninjured hand. This suggests that short-term amputation results in functional cortical reorganization, while the more permanent cortical changes after long-term amputation result from structural reorganization.

However, over 2 years, cortical reorganization after hand transplantation led to activation of somatosensory areas and an increase of activation in primary motor cortex, indicating a shift of neuronal activity back from the "programming area" to the executing SM1.

In contrast to hand replantation, the patient with hand transplantation failed to show any activation in the lateral premotor regions, which are known to process sensory information for certain movement parameters (Jackson and Husain, 1996; Wise et al., 1997), possibly due to the fact that these areas received insufficient input from somatosensory areas.

One could speculate that the delay between amputation and transplantation critically influences the reversibility to a normal cortical activation pattern. However, it is not known whether there is a "cut off" time between amputation and transplantation, after which motor recovery is unsatisfactory. We suggest that patients who are eligible for hand transplantation should be included pre-operatively in an extensive training programme, either with mental imaging of hand movements, which is known to evoke cortical activity in motor areas, or with increased use of a myo-prothesis.

Several caveats need to be mentioned with respect to this study. The observed results are based on one case each of transplantation and replantation; future cases may show different patterns of cortical activation and recovery due to age-related factors, variability of the individual extent of activation size, the circumstances of their hand lesion, the surgical procedure or post-operative factors. Furthermore, there may be differences between activation patterns following allografts and autologuous replantation. Although speculative, a difference in one of these factor might explain the much faster reorganization after bilateral hand transplantation found by Giraux et al. (2001).

Our data suggest that cortical reorganization after longstanding deafferentation and deefferentation is partially reversible, but that reorganization after hand transplantation continues for at least 2 years, whereas immediate replantation quickly restores a normal cortical pattern.

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