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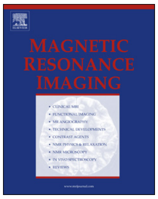

Motor and sensory cortical reorganization after bilateral forearm transplantation: Four-year follow-up fMRI case study

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ABSTRACT

The objective of this study was to characterize the cortical activity pattern of one patient who received bilateral forearm transplants.

Using fMRI we acquired motor and sensory brain activity every year after surgery and during three consecutive years while the patient underwent physical rehabilitation.

The motor related cortical activity evaluated during the first year showed a sparse pattern involving several brain regions. Over time, the analysis showed a progressive delimitation of the motor-related areas that had significant activity. The results also showed continuous size reductions of the activated cluster in the motor cortex. The activation in the sensory cortex showed significant increases in cluster size over time. The intensity of both motor and sensory cortical activations correlated with the Disabilities of the Arm, Shoulder and Hand questionnaire.

Our results show significant cortical reorganization of motor and sensory cortices after transplantation of bilateral forearm transplantation over a four-year period.

1. Introduction

Cortical reorganization after amputation is a well-known phenomenon resulting in decreased sparse cortical activity of the respective motor and sensory regions. Studies in primates have shown an increased representation of the adjacent cortical areas over the region that was used for the amputated limb [1]. Similarly, in human amputees the representation of the unaffected muscles expands to cover regions previously dedicated to the missing limb [2]. The few studies on the cortical reorganization after limb transplantation have reported shifting of the cortical representation and an increased activity in motor cortex [3,4,5]. To test the long term brain reorganization, here we explored the functional integration of bilateral transplanted upper limbs in an amputee patient by measuring the sensorimotor brain activation up to four years after the transplantation surgery.

2. Materials and methods

2.1. Patient

A 52-year-old man suffered a high-voltage electrical burn causing the loss of his hands in January 2011. The patient underwent bilateral proximal forearm transplantation in May 2012. The donor was a 34-year-old brain-dead multiorgan donor. After the transplant, the patient followed a comprehensive rehabilitation program [6]. The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire [7] was used to assess the evolution recovery in the patient. The protocol was approved by the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán ethics committee. The participant gave signed informed consent prior to the beginning of the study.

2.2. Imaging acquisition

Brain imaging sequences were acquired with a 3 T GE Excite scanner (GE Healthcare Technologies, Waukesha, WI) equipped with a standard quadrature head coil. The acquisition included a high-resolution inversion recovery spoiled gradient-echo T1-weighted isotropic, volumetric sequence (3D SPGR 1 × 1 × 1 mm^3, 180 slices

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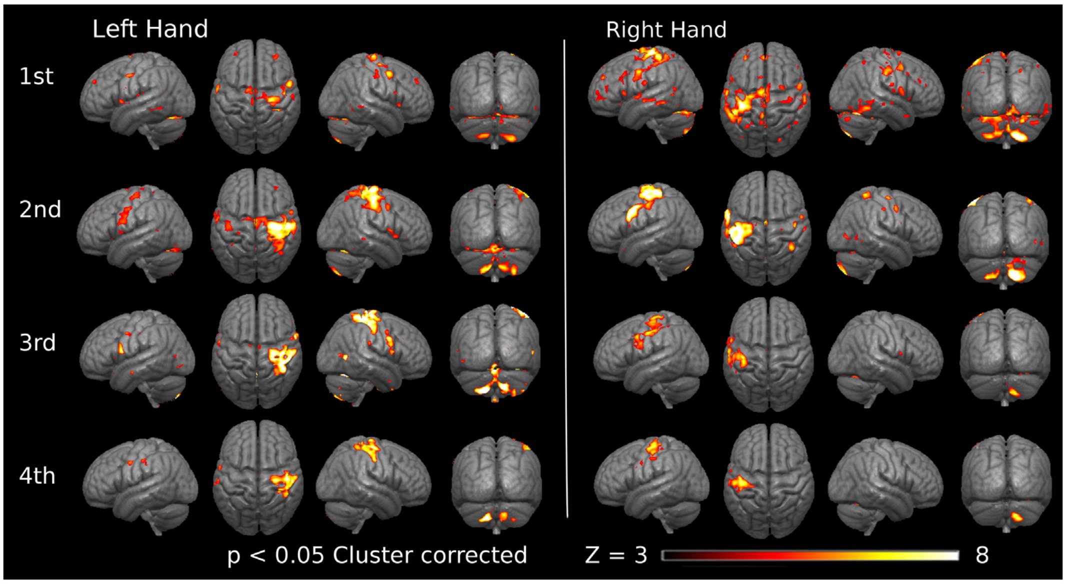

Fig. 1. Cortical activation during the movement of the transplanted hands. Rows indicate the time point of MRI acquisition across four consecutive years. In the top and posterior views the right hemisphere is represented on the right.

TE/TR/TI = 2/7/400 ms, flip angle = 15, matrix = 256 × 256 × 180, FOV = 240 × 240 × 180 mm^3) and four functional images using a gradient-echo single-shot echo-planar imaging sequence (repetition time 3000 ms, echo time 50 ms, field of view 200 mm, matrix 64 × 64, 39 slices of 3.75 × 3.75 × 4 mm thickness with no gap) of 120 volumes with whole brain coverage.

2.3. Stimulation paradigm

The patient was introduced to the scanner and instructed to relax and refrain from making head movements. Foam pads were used to better constrain head motion. Four functional images were acquired related to the right hand movement, left hand movement, right hand sensory stimulation, and left hand sensory stimulation respectively. Each functional run lasted 6 min, and comprised six resting blocks (10 volumes, 30 s.) interleaved with six stimulation blocks (10 volumes, 30 s.). Each run started with a resting condition. For the movement runs, the patient was asked to move his fingers with a regular motion (~3 Hz) during the stimulation block period, using and expansion/contraction movement avoiding motion of other parts of his body. For the sensory runs the experimenter brushed the patient's fingers with a rouge sponge with regular motion (~3 Hz) during the stimulation block period.

2.4. Data analysis

fMRI data processing and statistical analysis were carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following preprocessing was applied: motion correction using MCFLIRT [8]; non-brain removal using BET [9]; spatial smoothing using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 30.0 s). Time-series statistical analyses were carried out using FILM with local autocorrelation correction [10]. Z Gaussianised statistic images were thresholded using clusters determined by $Z > 5.0$ and a (corrected) cluster significance threshold of $p < 0.05$. Registration of the functional images to high resolution structural and standard space images was carried out using FLIRT [8]. All analyses were performed in the original patient space; for visualization proposes the final activation maps were warped into the standard space (Montreal Neurological Institute MNI152 template) and rendered to create a 3D representation of the brain activity. For each time point and task, the peak activation t value and cluster size were obtained. Linear regression was calculated between the DASH score and the activation radio. The activation radio represents the relationship between intensity and size of the activity in the whole brain, and was determined dividing the t value over the number of voxels showing significant activation in each task.

3. Results

3.1. Motor task

The cortical activation during the motor task showed a similar progression pattern for both hands (Fig. 1). During the first time point the cortical activation showed a widespread pattern with peak activity in the ipsilateral cerebellum and the contralateral motor cortex. However, activity was also found in the supplementary motor area, contralateral cerebellum, ipsilateral motor cortex, and bilateral sensory, temporal and frontal cortices. The second time point revealed a reduction in activation that resulted in better defined clusters in the contralateral motor cortex and bilateral cerebellum. It also leads to smaller activation clusters in the ipsilateral motor cortex and bilateral sensory cortex. The third time point showed further concentration of the activity to the corresponding expected areas, with significant peak activity only in the contralateral motor cortex and the ipsilateral cerebellum. The last time point after 4 years of the limbs transplants showed well defined patterns of activity in the contralateral motor cortex hand area and in the ipsilateral cerebellum. The left hand movements resulted in lower activations compared to the right hand movements. However its activation pattern followed a similar progression to the right hand with the exception of the cerebellum which showed bilateral activity during the four scans. For the peak activations coordinates and cluster sizes of each time point see Table 1. The activation ratio for each time point correlated with the DASH score in both hands (right

Table 1
Coordinates of cortical peak activations for each time point for each task.

Task	Time point	BA	X	Y	Z	T	CSP
Right hand movement	After surgery	3	−34	−26	68	8.84	2291
	1 year	4	−40	−16	64	9.22	2139
	2 years	4	−38	−14	64	7.56	973
	3 years	4	−40	−16	62	8.51	715
Left hand movement	After surgery	3	26	−22	72	7.54	1838
	1 year	4	36	−20	70	8.64	3011
	2 years	6	58	−6	74	8.24	195
	3 years	4	44	−16	62	12.8	7142
Right hand sensory	After surgery	5	−40	−36	68	7.54	83
	1 year	40	−44	−32	62	9.03	1110
	2 years	2	−40	−30	68	10.5	1786
	3 years	3	−60	−18	44	12.6	5236
Left hand sensory	After surgery	5	36	−40	68	6.04	35
	1 year	3	38	−24	72	13.7	3545
	2 years	2	52	−20	60	12.4	2601
	3 years	2	52	−16	34	13.3	5281

Note. Coordinates in MNI space in millimeters. BA = Brodmann area; CSP = cluster size of peak activation (voxels).

hand movement $R^2 = 0.93$; left hand movement $R^2 = 0.66$) see Supplementary Fig. 1.

3.2. Sensory stimulation

Cortical activation during sensory stimulation for both hands showed a similar progression pattern (Fig. 2). During the first time point there were small activation clusters in sensory related areas. At the second time point the activation in the contralateral sensory cortex and in the ipsilateral cerebellum showed a large increase, revealing well-defined clusters. The third time point did not show major changes of activity. The last time point at the fourth showed a small expansion in the activity but new clusters appeared in the ipsilateral motor cortex. After the first time point the cortical activation was higher in the left hand compared to the right hand. For the coordinates of peak activation and cluster size of each time point see Table 1. No correlation was found between the activation ratio and the DASH score for each individual hand. However, further analysis combining bilateral activation showed a strong correlation with DASH score (bilateral hand sensory $R^2 = 0.84$) see Supplementary Fig. 1.

4. Discussion

In this study we characterized the cortical reorganization changes of the motor and sensory cortices in a patient after bilateral forearm transplantation and four years of rehabilitation. Our results showed a reconstitution of the activation within the motor cortex as well as the cortical incorporation and expansion of activation area in the sensory cortex.

4.1. Motor cortex

The pattern of activity in the motor cortex showed a well-defined reduction of the area involved in the hand movement across the three years rehabilitation. After surgery the activity was spread over many areas of the brain, suggesting the possible recruitment of several brain areas to achieve the desired movement of the new hand. The patient spent more than one year waiting for a transplant,

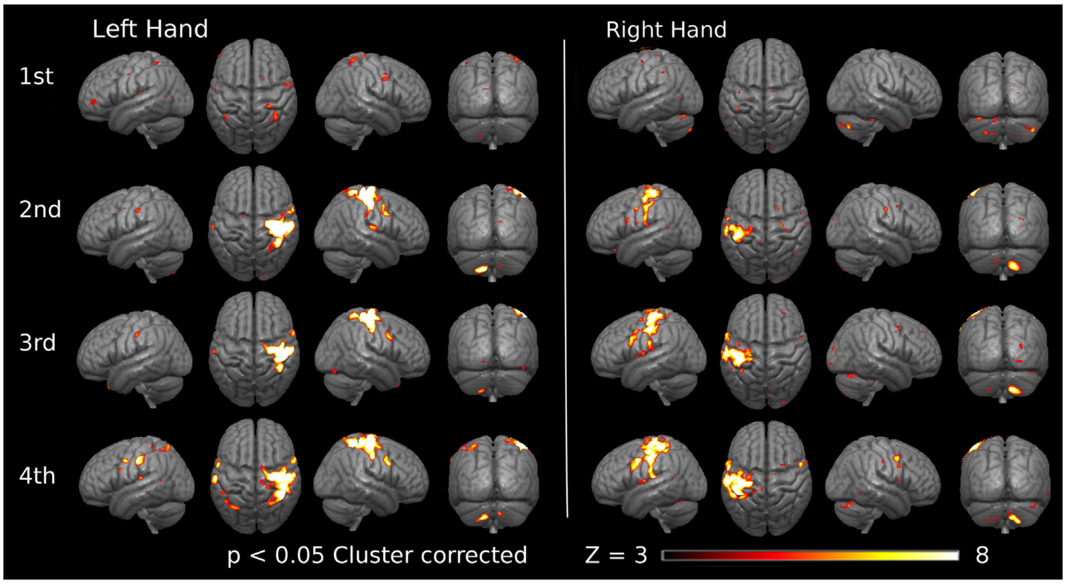

Fig. 2. Cortical activation during sensory stimulation of the transplanted hands. Rows indicate the time point of MRI acquisition across four consecutive years. In the top and posterior views the right hemisphere is represented on the right.

presumably resulting in some cortical reorganization of the areas related to the lost limbs [2]. It is important to note that the main activation on the first acquisition had its peak in Brodmann's area 3 (postcentral gyrus) for both hands (Table 1). After the second acquisition the peak activity shifted to primary motor cortex. Our results support the reversibility of this previous reorganization showing that the activity of the movement of the hand shifts and restricts to a very specific area in the motor cortex. Our results show motor activity reconstitution after three years of rehabilitation, when the patient has recovered most its new hands functionality as measured by the DASH questionnaire.

4.2. Sensory cortex

The cortical response to sensory stimulation of the hands showed significant changes across the three years of the study. As expected, after one year of the surgery we found few small clusters of activity showing minimal activation in the sensory cortex. However, from the second year and on, the analyses showed well defined clusters of activity that kept expanding through the years. Our findings are supported by a previous case showing the cortical reorganization of one patient after his hand was replanted [11]. This study showed that after one year, the patient recovered sensibility was accompanied by large cortical activations in the sensory cortex. Our results advance those findings by showing that transplanted limbs also result in cortical activation when stimulated, even after more than one year or nerve deprivation. The increase in the responsive cortical area over the years may be related to either larger innervation of the limbs, or better integration of the sensory information coming from the transplanted limbs. Future studies should be designed to delve into those possibilities.

5. Conclusion

Our study shows the progression of the cortical activity reorganization in the motor and sensory cortices during a four year period after bilateral arm transplantation. This analysis showed a progressive delimitation of the motor-related areas showing significant activity as well as a reduction of the cluster size in the motor cortex. In contrast, the activation area in the sensory cortex increased over time. Overall, our results show a better characterization of the cortical reorganization after rehabilitation and a correlation between cortical activity and the clinical scores.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.mri.2015.12.025.

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