Reorganization in the Primary Motor Cortex after Spinal Cord Injury - a functional Magnetic Resonance (fMRI) Study

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Keywords

Spinal cord injury, cortical plasticity, reorganization, functional Magnetic Resonance Imaging (fMRI), primary motor cortex

Abstract

Activation maps in the primary motor cortex (M1) were investigated in three patients with complete spinal cord injury (SCI) at the level of TH3, TH7 and TH9 and in one patient with an incomplete spinal cord injury at the level of L1 during right elbow (4 patients), right thumb (4 patients), bilateral lip (2 patients) and right foot (3 patients during imagined, 1 patient during executed) movements using functional Magnetic Resonance Imaging (fMRI). Compared to control fMRI activation maps of patients with complete paraplegia showed a cranial displacement of the activation maxima in the contralateral primary motor cortex during elbow movement of 13.3 mm, whereas the maxima of thumb and lip movements were not altered. The patient with an incomplete spinal cord injury revealed no displacement of elbow activation maxima. The reorganization is likely occurring on the cortical and not on the spinal level.

Introduction

Cortical plasticity and cortical reorganization reflects the ability of the cortex to adapt to changing conditions [1]. After complete peripheral neural injury a shift of adjacent somatotopic representations into the deafferentiated area in the contralateral primary motor (M1) and sensory cortex (S1) has been shown by different methods. Pons et al. [2], using electrical cortical mapping in monkeys with long lasting (> 10 years) upper limb deafferentiation, observed a contralateral shift of sensoric face representation into the area of the deafferentiated limb. For patients with spinal cord injuries, occurring 2 to 20 years ago, Topka et al. reported an enlargement of cortical maps of targeting muscles proximal to the injury using transcranial magnetic stimulation [3]. An expanded cortical map was also reported by Streletz et al. [4] for the musculus biceps brachii in patients with complete lesions of the cervical spinal cord (C5-C6) within 6 to 17 days after injury.

As the determination of cortical activation sites with Positron Emission Tomography (PET) is hampered by low spatial resolution, details in the functional organization of the cortex cannot be analyzed [5]. In addition overlaps of representation areas have been reported for elbow and hand movements as well as for different finger movements [6,7] evaluating significant activation with fMRI. With fMRI a spatial resolution of up to 2 mm can easily be achieved, and therefore it is possible to evaluate cortical activation during voluntary tasks and to detect even small displacements of somatotopic representation in M1 and S1.

In our fMRI study we were interested to determine whether a displacement of functional activated areas into the deafferentiated region occurs in contralateral M1 in patients with complete and incomplete spinal cord injuries. As recent fMRI reports [8] have shown a significant M1 activation during motor imagery, we have tried to map the deafferentiated area by an imagination task of foot movement, to determine the M1 location and possible alterations in SCI patients.

Methods

Patients and Subjects:

Four patients with SCI were investigated (3 male, 1 female; mean age 53.7 years). Demographic data and American Spinal Injury Association (ASIA) motor score [9] for all patients and controls are given in Table 1. Three patients had a complete, one patient an incomplete spinal cord injury. The level of the lesions were TH3, TH7 and TH9 for the complete SCI and L1 in the incomplete SCI patient. Twenty healthy subjects (16 male, 4 female, average 29 years) with no neurologic impairment were investigated for fMRI activation maxima (AM) during feet (lifting the right foot, n = 5), elbow (flexion and extension, n = 5), thumb (flexion and extension, n = 5) and lip (lip puking, n = 5) movements and served as a control group. Prior the experiments the study design was approved by the local medical ethics committee.

-------- Insert Table 1 about here -------

Measurement:

fMRI was performed with a Siemens 1.5 Tesla Scanner using echo planar imaging (EPI: matrix 96*128, FOV 250 mm, TE 59 ms, scan time 7 sec, repetition time 10 sec) of the whole brain with 36 slices of 3 mm slice thickness and 1 mm gap. Healthy subjects were measured with 45 contiguous slices of 3 mm slice thickness. 48 measurements (units of six measurements during each movement with alternating rest and activation four times) were performed per each condition. Additionally corresponding anatomical T1-weighted images and a T1-weighted 3D- dataset with 128 sagittal slices (Matrix 256*256, slice thickness 1 mm) were acquired to display activated areas on the brain surface.

The patients and subjects were lying supine with their eyes closed in the scanner. The head and the proximal limb were securely fixed to minimize involuntary movements. Cortical activation during right elbow (4 patients), right thumb (4 patients), lip (2 patients) and imagined (3 patients) and executed (1 patient) right foot (lifting the foot) movements were measured by fMRI. All

movements were externally paced by a metronome: executed tasks with a rate of 60, imagined tasks at a rate of 40 movements per minute.

Statistical data evaluation:

fMRI data were evaluated using the statistical parameter mapping program (SPM' 96, Wellcome Department of Cognitive Neurology, [10]). fMRI scans of each subject were realigned to correct for interscan movement artifacts. After manually defining the anterior comissure as reference point, the image sets of each subject were coregistered to the anatomical datasets. The EPI-data were smoothed with a Gaussian filter of 10*10*6 mm for individual comparisons. Statistical significant differences between movement and rest were assessed using the delayed box car model by a z-tests ($p < 0.01$). This procedure was the same for the data of normal subjects and patients.

An accurate spatial differentiation of the individual cortical activation in the whole data-set was made possible by a custom-made projection method, for which the activation maps were prior superimposed on the 3D-MRI dataset. From an individually selected center an ellipsoid shell, cutting a 20 mm thick section beginning from the surface of the cortex, was fitted to the individual brain, to display the cortical relief and the functional activation of each subject (Figure 1). Distances from the crossing of interhemispheric fissure with the central sulcus and the activation maxima in M1 were measured using the Euclidian distance along the surface of the selected ellipsoid.

For interindividual comparison of somatotopic representation and possible displacement of activation maxima in patients, distances from the central crossing point to the activation maxima were expressed as length of the precentral gyrus in percent. To this end, the total length of precentral gyrus from the central crossing point to the sylvian fissure was individually determined and the location of activation maximum calculated in percent relative to the total length (activation distance * 100 / individual length of the precentral gyrus). The average length (105.2 mm, n = 20, standard deviation (SD) = 7.5 mm) of the precentral gyrus approximates the length of normalized precentral gyrus (100mm). The relative length in % was calculated as absolute length in mm by multiplication with 1.052.

Evaluation of statistical significance of displacement in patients compared to

controls was carried out with the following procedure: The distances from the central crossing point to the AM were determined in normal subjects and the physiologic range of somatotopic activation was limited to 2 SD ($p<0.05$) outside the average activation maxima.

Results

The results for each patient and the averaged data for the controls are given in Table 2. The AM of patients with complete and incomplete SCI during movement of muscle groups, which are represented distinct to the deafferentiated area in the left precentral gyrus (lip, right thumb), were found within 1 SD compared to normal subjects (see Tab. 2) and therefore regarded not to be different to normal (patients with complete SCI: 1.4 % (1.5 mm), patients with incomplete SCI: 3.2 % (3.4 mm)).

-------- Insert Table 2 about here -------

However, contralateral AM of elbow movements (biceps brachii muscle) in complete SCI patients were significantly displaced 12.6 % (13.3 mm) into the direction of the disconnected M1, while in the patient with an incomplete SCI no significant change in elbow representation was observed (difference: 2.4 % (2.5 mm); Fig. 1 and 2).

-------- Insert Figure 1 about here -------

Finally, imagined movements of the right foot failed to show a significant M1 activation in all patients with a complete SCI. In the patient with an incomplete SCI no displacement of AM during executed movements of the right foot was found compared to controls.

-------- Insert Figure 2 about here -------

Discussion

While cortical reorganization in subjects with unilateral deafferentiation, like in upper limb amputees [11], may be analyzed by comparison of activation patterns of the unaffected and affected M1 and S1, assuming that motor representations for both sides are symmetrical, as shown for normal subjects, the analysis of reorganization in patients with SCI can only be achieved by a comparison to a control group or by mapping the somatotopic representation prior and after the lesion occurs. As we were not able to investigate our patients prior to trauma we compared cortical representation maps of SCI patients to control subjects. Location shifts of activation maxima during a standardized movement of patients compared to controls were considered significant, if they exceeded two times of the standard deviation of normal subjects.

Activation maxima (AM) represent the location of the highest z-score of a representation map in the precentral gyrus. Although mapping the AM shows some disadvantages (AM does not describe the shape of an activation cluster) compared to the description of "whole representation maps“, the AM-mapping method is threshold independent. The threshold of significant activation (in our study $p < 0.01$) only excludes non-significant activation for the evaluation of activity in the motor cortex. A simple three dimensional description of representation maxima is not possible. Describing representation maps by their "center of gravity" shows the disadvantage of threshold dependence. A comparison of the group data of patients and of normal subjects using the Talairach coordinates of AM in an activation cluster is commonly used to map representation areas in fMRI and PET studies. However, a precise differentiation of activation in the pre- and postcentral gyrus is not possible because normalization after Talairach shows a spatial insecurity of more than 2 cm for the central sulcus (see also [12]). Therefore we developed a new method, projecting the activation maps and the anatomic data on a two dimensional circle and evaluated only the location of activation maxima in the precentral sulcus assuming, that this anatomical structure is representing M1.

Imagined foot movements showed no significant activation in the precentral gyrus in all patients. Imagination of hand movements in normal subjects is known to cause significant activation in M1 (i.e. [8], [12]). The same holds true for patients with upper limb amputation, where a significant M1 activation of the former hand area during

imagined movement was reported [11].Unlike upper limb amputees, patients with SCI already mentioned before scanning, that they were not able to imagine movements of their deafferentiated feet. Since we did not control for other psychological variables (i.e. representation of the body) we can only speculate on these finding. We assume that imagination of foot movements is not suitable for mapping deafferentiated areas in M1 in SCI patients.

We observed a shift of AM during elbow movements in the direction to the disconnected area in complete SCI patients. The average shift of AM during elbow movements in patients with complete SCI was with 7.8 % of precentral gyrus length (8.2 mm) more then two SD outside of the normal AM representation range.

Topka et al. [3] using TMS showed signs of reorganization for cortical representation of abdominal muscles, that are proximal to the lesion. In our study we also selected two muscles proximal to the lesion: abductor polices brevis (APB) for thumb movement (C7/8), and biceps brachii (BB) for elbow movement (C5/C6), with BB being more distant to the spinal level of lesion as APB (see also [4]). However, on the cortical level BB is located adjacent to the cortical disconnected area and revealed reorganization phenomena whereas APB showed no difference in location compared to controls. These findings suggest that reorganization is likely to take place at cortical and not at spinal level.

TMS data of patients with spinal cord injury showed enhanced excitability of representation areas adjacent to the deafferentiated cortex area whereas the disconnected area does not react on TMS [3, 4]. We observed a cranial displacement of activation maxima during elbow movements in SPI patients by fMRI.

This displacement of AM in complete SCI patients is interpreted as reorganization of the primary motor cortex. The underlying mechanisms of reorganization are unclear. Taking into account previous studies on posttraumatic and temporary reorganization (i.e. [13, 3, 4]) we think, that functional reorganization of motor cortex is more likely generated either by lack of lateral inhibition or possibly by atrophy of axotomized pyramidal neurons or both than sprouting. Since an enlarged cortical map for APB was already reported in patients 6 to 17 days after complete C5 spinal lesion, an unmasking of preexisting synapses seem to be more likely than an increase of intact neural dendrites over time [4]. Interestingly fast changes in cortical representation

have been shown already after local anesthesia within the time limit of minutes (i.e. [14].

For further studies it would be interesting, how activation maxima and maps of representation areas adjacent to the deafferentiated area change in incomplete SCI patients during the clinical follow up. Using TMS first results were already reported for SCI patients describing a decrease of excitability in cortical areas adjacent to the de-afferentiated area correlating to clinical improvement [15].

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Legends

Table1: Demographic data of patients participating in the study with patient number, age, level and completeness of spinal cord injury (SCI).
row 3: etiology of SCI
row 4: the duration since the injury occurred in weeks
row 5: the ASIA motor score (100: motor function not impaired [9])

Table 2: Results of patients and control subjects with distance of activation maxima in % in left M1 for lip, thumb and elbow movement with mean and standard deviation for patient 1-3 (complete SCI), and the averaged values and minimal and maximal values for 5 subjects.

Fig. 1: fMRI activation maxima maps during elbow movements from single subjects with the ISOVIEW projection method shown in the left upper side. From an individually selected center an ellipsoid shell is fitted to the individual brain and cuts a 20 mm thick section through the cortex. The projections with elbow movement are shown for one single subject of each group; Upper right: normal subject (average distance 45.0%), lower left: patient with incomplete SCI (distance 42.6%) and lower right: patient with complete SCI (average distance 32.4%). The line indicates the distance from the „central crossing point“ to the activation maximum in the precentral gyrus.

Figure 2: fMRI activation maxima in all patients. Left incomplete SPI and right complete SPI during elbow (black E) and thumb (white T) movement. The absolute activation maxima are overlayed on the anatomical surface and marked with white circles. Distances determined from crossing of precentral gyrus with the interhemispheric fissure to the AM are shown as white lines and plotted at the bottom for each patient in %.

patient # **age (years)** **SCI**	**1** **66** **complete**	**2** **41** **complete**	**3** **42** **complete**	**4** **66** **incomplete**
level	TH3	TH7	TH9	L1
etiology	ependymoma	trauma	meningioma	AV-malform.
duration	12 weeks	1456 weeks	6 weeks	52 weeks
motor score	50	50	50	76

Table 1; Lotze et al.

Patient #	1	2	3	mean, # 1-3 mean (SD)	4	control, n = 5 mean (SD)
fMRI lip	-	84.8	67.2	76 (12.4)	-	73.7 (4.2) min: 68.5 max: 78.1
fMRI thumb	45.0	48.8	54.2	49.3 (3.8)	51.1	46.8 (5.2) min: 43.0 max: 57.0
fMRI elbow	34.0	29.4	33.9	32.4 (2.6)	42.6	45.0 (2.4) min: 42.0 max: 49.0

Table 2; Lotze et al.

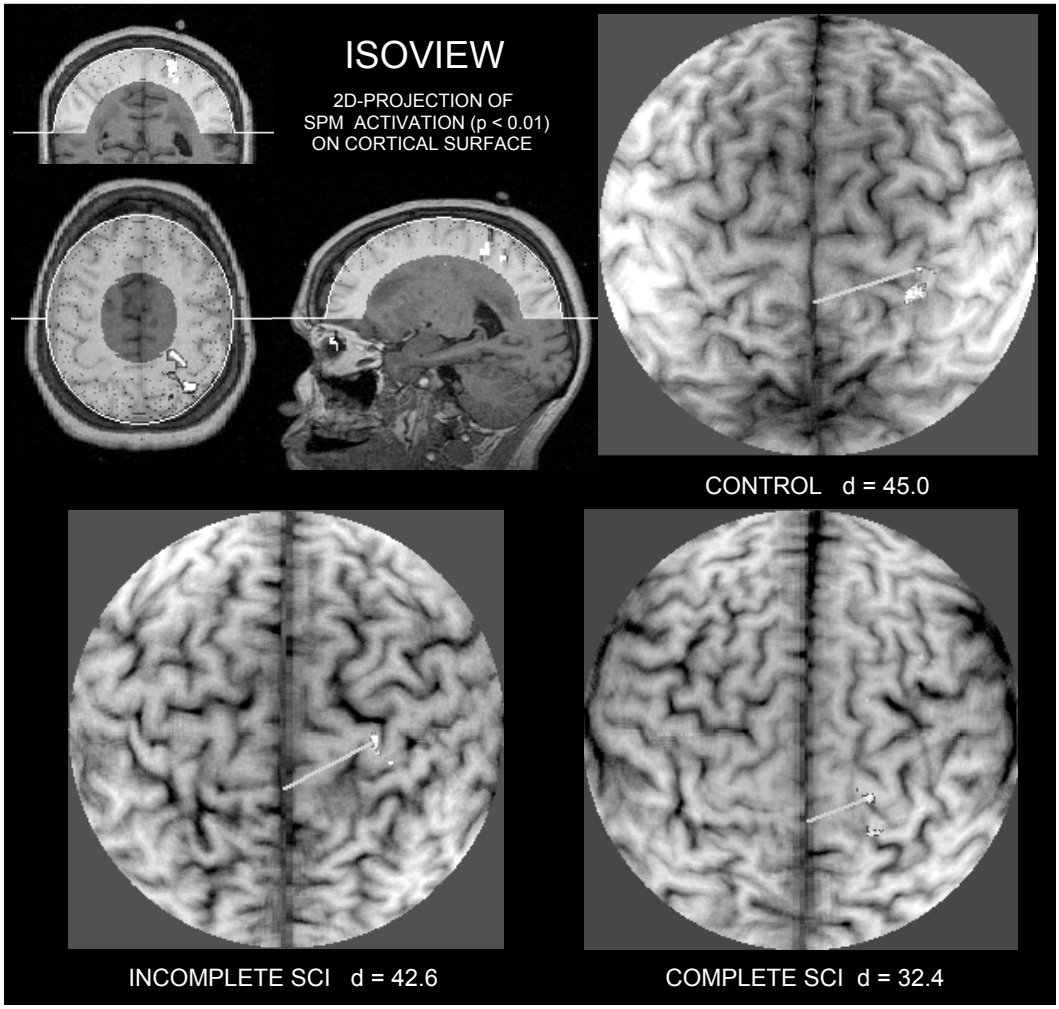

Figure 1; Lotze et al.

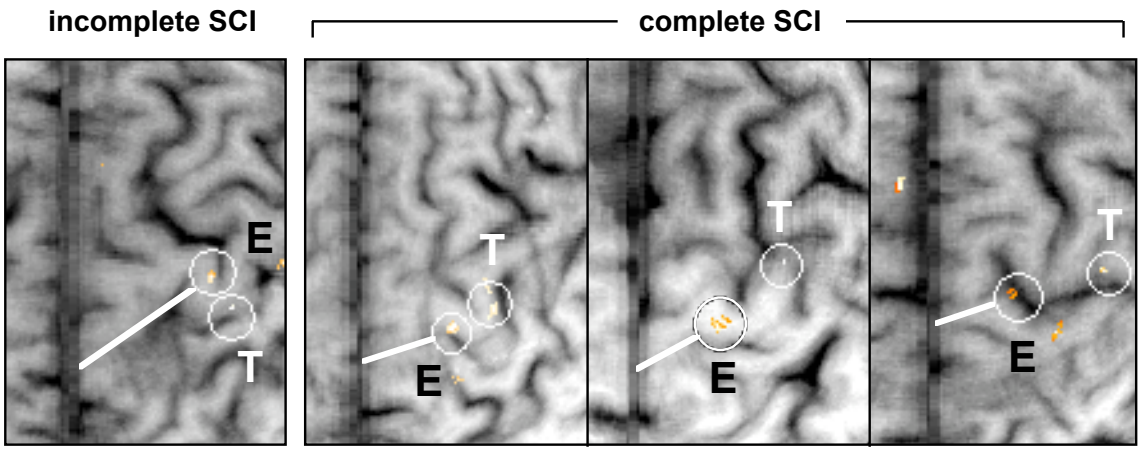

Figure 2; Lotze et al.