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Combination of TMS and fMRI reveals a specific pattern of reorganization in M1 in patients after complete SCI

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Abstract. *Purpose:* After a spinal cord injury (SCI) which was complete deafferentation of the body representation caudal to the lesion height results in drastic changes in the cortical representation. The underlaying processes are incompletely understood.
Methods: We investigated cortical representation sites of upper limb muscles using functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) in five patients suffering from thoracic complete SCI and one with an incomplete SCI in the height of L1.
Results: In comparison to healthy controls fMRI demonstrated a displacement of elbow movement representations in the precentral gyrus in patients with complete SCI into the direction of the deafferented cortical thoracic representation. Changes increased with time after the incidence of SCI. TMS revealed reduced excitability and prolonged silent periods for muscles more distant to the deafferented area.
Conclusions: Whereas fMRI demonstrated changes in representation sites adjacent to the deafferented area, TMS excitability changes were also observed more distant to the deafferented area and silent periods were prolonged in comparison to healthy controls. TMS changes might depend on both: the distance to the deafferented area and the time of persistence of deafferentation.

Keywords: SCI, reorganization, amputation, cortical plasticity, deafferentation, motor

1. Introduction

After a thoracic spinal cord injury (SCI) large areas within the somatosensory cortex are deafferented and areas within the primary motor cortex are deefferented to the descending motor system. As a consequence, these patients undergo substantial changes in the neural representation of the body, associated with alterations in the location of cortical representation sites and in cortical excitability. Altered input-output patterns induced by spinal cord injury are accompanied by reorganization of the cerebrum as demonstrated by imaging studies. Studies using Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) indicated an enlargement of cortical representation sites even in regions quite distant from the deafferented site (for hand representation [1], for fingers [2], for tongue [3]). Cortical representations

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adjacent to the deafferentation area show a shift of their activation maxima into the direction of the deafferented area in comparison to those of healthy controls (thoracic complete SCI: biceps brachii [4]; cervical complete SCI: tongue movement [3,5]).

While PET and fMRI studies render important information to the topography of post-lesional changes in the cerebrum, these techniques are not suited for evaluating an excitatory or inhibitory effect of underlying changes in activation patterns. Transcranial Magnetic Stimulation (TMS) is capable to provide evidence for this. Previous TMS studies in SCI patients reported increased excitability at rest in muscles adjacent to the cortical deafferented area, suggesting post-lesional motor reorganization in adults. Levy et al. [6] found enlarged motor cortical representation maps of two unaffected arm muscles immediately adjacent to the level of SCI in two quadriplegic patients. Topka et al. [7] investigating patients with thoracic SCI demonstrated increased representation maps, larger amplitudes of Motor Evoked Potentials (MEPs) as well as shorter latencies in unaffected trunk muscles innervated superior to the height of the spinal lesion and represented adjacent to the cortical deafferentation area. In another TMS-study Laubis-Herrmann et al. [8] reported reorganization for an arm muscle represented near to the deafferented area but not for another arm muscle represented more distant to the deafferentation area caused by a SCI at the thoracic height. In contrast to findings of Topka et al. [7] a decrease of excitability in these muscles was observed.

Studies with healthy volunteers demonstrated spatial differences between the location of motor representation between TMS and fMRI, which varies between 0.5 and 1.8 cm [9–12]. Although, both methods are suitable for mapping motor representations, they differ in the way of mapping: fMRI evaluates active movements whereas during TMS movements are elicited passively during rest or during facilitation.

By combining fMRI and TMS in the same patients suffering from SCI we intended to address the following questions:

1) Are there differences in representation sites adjacent or more distant to the deafferented area and in which way is cortical excitability of these muscles altered in patients compared to healthy controls?
2) Do findings obtained with fMRI on cortical motor representation, findings obtained with TMS on motor cortical excitability and clinical data correlate in patients who experienced a thoracic SCI?
3) Is the combination of both methods in the same patients helpful to understand partially contradictory reports about reorganization after complete SCI?

2. Methods

2.1. Subjects

We studied 5 patients (39–66 years, mean: 44.4; SD: 5.0; 2 female) with complete thoracic or lumbar SCI and one with an incomplete L1-lesion (66 years; male). TMS-measures were performed prior to fMRI which followed immediately afterwards. None of the patients had severe craniocerebral trauma or skull defects. Six healthy volunteers with no neurologic or psychiatric impairment (39–60 years, mean: 45.2; SD: 3.4; two female) served as a control group. The study was approved by the ethics committee of the University Hospital of Tuebingen. All subjects gave written informed consent prior to participation in the study. The extent of motor and sensory impairment was evaluated using the classification scale of the American Spinal Injury Association (ASIA), including the ASIA-Impairment-Scale (IS) and the ASIA-Impairment-Scores: Motor-Score (MS) and Total-Score (TS [13]). Patients' relevant clinical data are summarized in Table 1.

2.2. Experimental procedures

2.2.1. TMS

The subjects lay supine on a bed in a quiet room during the experiments. Focal single-pulse TMS was delivered to the left motor cortex through a custom-made poly-foam coated figure-of-8 coil (diameter 2 x 70 mm, 9 turns of wire, peak magnetic field strength 2.2 T, peak electric field strength 660 V/m) that was connected to a magnetic stimulator (Magstim Rapid, 2 booster modules, The Magstim Company, Spring Gardens, Whitland, UK). Using surface electrodes, EMG activity was recorded from either one or the other of the two target muscles of the right arm proximal to the lesion (M. abductor pollicis brevis (APB) and M. biceps brachii (BB)). Each target muscle was investigated separately. EMG activity was recorded at a digitizing rate of 5000 Hz using a Toennies electromyography system (Toennies, Myograph II), digitized and stored on a personal computer. During the data acquisition, MEPs were displayed on the oscilloscope screen at a sensitivity of 100 μV/div (50 μV/div) during determi-

Table 1

Code	Age (years)	Gender	Nature of injury	Time of injury (weeks)	Motor impairment below	SCI[1]	ASIA-IS[2]	ASIA-TS[3] (points)	ASIA-MS[4] (points)
1	66	f	angioma	12	Th 3	comp	A	100	50
2	41	m	vertebrae fracture	1456	Th 7	comp	A	108	50
3	42	m	meningioma	6	Th 9	comp	A	112	50
4	34	f	vertebrae fracture	896	Th 11	comp	A	120	50
5	39	m	direct trauma	1776	Th 7	comp	A	112	50
6	66	m	AV-fistula	52	L 1	incomp	C	155	76

[1]SCI: spinal cord injury: comp: complete; incomp: incomplete.
[2]ASIA-Impairment-Scale (ASIA-IS): A = complete lesion with no motor or sensory function preserved in S4/5 segments; C = incomplete lesion with at least half of the key muscles below the lesion having a grade < 3; according to the British Medical Research Council.
[3]ASIA-Total-Score (-TS): max. 212 points (no impairment).
[4]ASIA Motor-Score (-MS): max. 100 points (no impairment).

nation of motor thresholds. Off-line analysis of EMG recordings included digital filtering using a 50 Hz bandstop and a 200 Hz lowpass filter and manual determination of MEP latencies as well as peak-to-peak MEP amplitudes.

For each target muscle, motor thresholds (MT) at rest and during facilitation of voluntary activation of the target muscle were evaluated. Recruitment Curves (RC) were measured for the resting and the facilitated condition. To determine MTs, TMS was delivered to optimal scalp positions for excitation of MEPs, while muscles were at rest using the method reported by the IFCN committee [14]. The coil was positioned tangentially to the scalp surface at a 45° angle with reference to the nasion-inion-line and the handle pointing laterally. The current induced in the brain was therefore directed approximately perpendicular to the line of the central sulcus, a condition optimal for activating the corticospinal system trans-synaptically [15, 16]. Muscle activity was monitored with a loudspeaker connected to the recording unit. For facilitated recordings of APB, subjects were instructed to gently press their right thumb and index fingers together; for BB subjects lifted a weight of 160 g with their right hand. For evaluation of the excitability of motor cortical representation areas of target muscles, we used RCs instead of cortical mapping since RCs appear to provide to some extent similar information about motor cortical excitability than mapping techniques [17]. The method for obtaining RCs for the active and resting condition has been described previously [8]. For evaluating RC for each stimulus intensity (100, 125, 150, 175 and 200%) eight stimulations were applied in random order at the maximal MEP-site of each target muscle. Silent periods (SP) following MEPs were measured for 140% and 180% of MT respectively and eight stimulations for each intensity were applied randomly. This was performed to elicit SPs which should be comparable between subjects since they were performed in a broad intensity range. SP-durations were measured from the end of the preceding MEP to the beginning of first reappearing continuous EMG-activity $> 50\ \mu$V [18]. In order to differentiate spinal and peripheral from cortical effects we measured the M-response and the F-wave for the APB in all subjects using the method reported by the IFCN committee [14].

2.2.2. fMRI

Highest MEP-site of the cortical representation areas of the two muscles where indicated with lipid vitamin-E capsules prior to fMRI [11]. The subjects lay supine with their eyes closed in the scanner. Head and proximal limb were fixed to minimize involuntary movement. Cortical activation during movement of the two target muscles was measured (right elbow movement: elbow flexors including BB; 45 degrees against gravity and extension with gravity; right thumb movement: muscles of the thenar eminence including APB; flexion and relaxation). Forty-eight measurements (units of six measurements during each movement with alternating rest and activation four times) were performed for each condition. The movements were metronome-paced with 1 Hz. 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 thickness and 1 mm gap. Additionally, T1-weighted anatomical data sets (FLASH, effective thickness 1.5 mm; matrix 224 * 256; FOV 250 mm; TR 9.7 ms) were acquired to display activated areas on the brain surface.

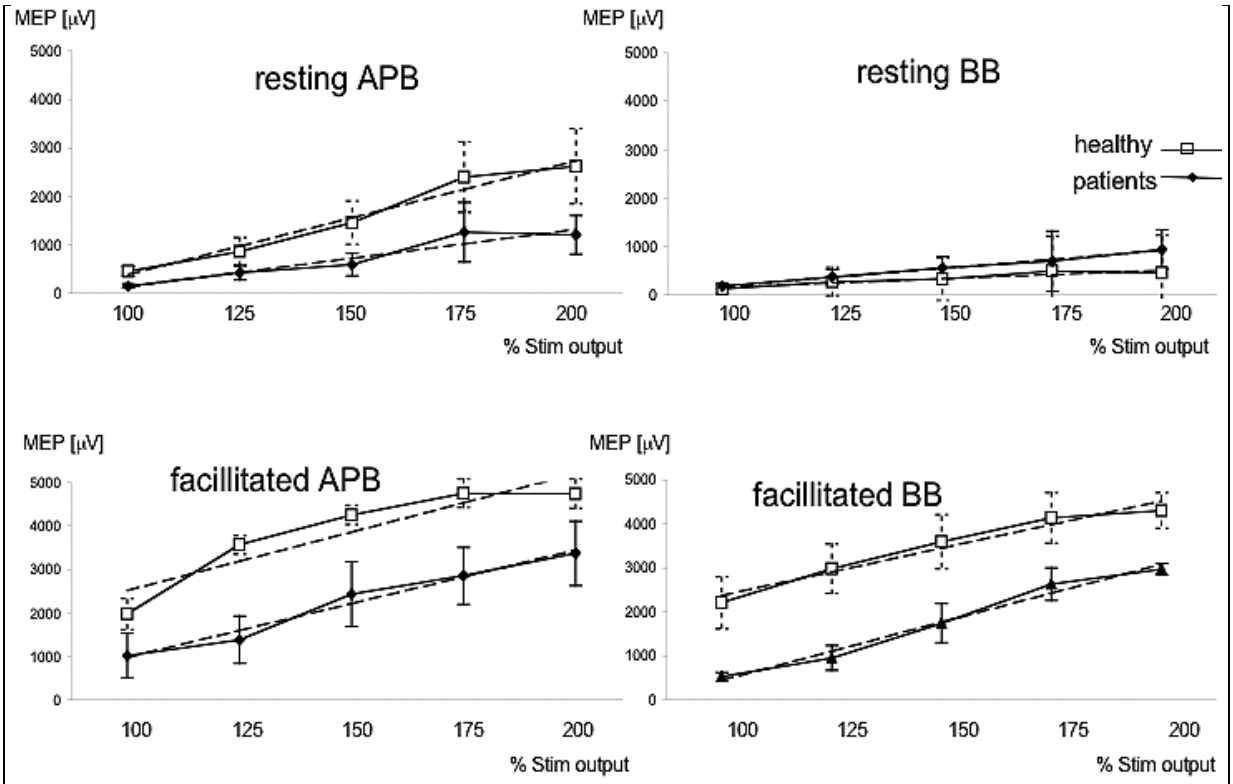

Fig. 1. Recruitment curves for averaged MEP's of patients with complete SCI and healthy controls. Bars indicate standard errors. Top row: recruitment evaluated during rest; bottom row: recruitment curves during facilitation; left: results for the abductor pollicis brevis muscle (APB), right: for the biceps brachii muscle (BB). Significant differences between patients and healthy controls were only observed during facilitation; MEP-amplitudes at rest did not significantly differ.

2.3. Statistical analysis

2.3.1. TMS

Motor thresholds in patients and controls were compared with independent t-tests.

Recruitment curves and silent periods were compared with a general linear model (GLM; Greenhouse-Geisser correction) using a repeated measurements analysis with the following factors: muscle (APB or BB), facilitation (rest or facilitated) and intensity of magnetic stimulus (100%, 125%, 150%, 175% and 200% of MT). Significant main effects and interactions were followed by post-hoc tests corrected for multiple comparisons (Bonferroni-correction). All statistical comparisons were performed with the Statistical Package for the Social Sciences (SPSS 10.05).

Slopes of recruitment curves were plotted using a linear regression fitted with Excel (Microsoft, 1992–2002; Fig. 1). Pearson correlations were performed between the following clinical, TMS and fMRI parameters: time since lesion; MT; slope of the recruitment curve; z-value of the highest activated voxel; location of activation maxima; number of activated voxels.

2.3.2. fMRI

The method of fMRI-evaluation and some of the data have been already described elsewhere (SCI patients [4]; HC [11]). After individual data evaluation using SPM (Wellcome Institute of Cognitive Neuroscience, London, UK) including realignement and smoothing (6 mm), activation above a height threshold of $p < 0.001$ and a corrected spatial extent threshold at $p < 0.05$ (FWE) were assessed. Individual image files with thresholded statistical parametric maps were written and were used for further data evaluation in the projection. For the evaluation of distances with the 2D-projection method, activation maps were superimposed on the 3D-MRI-datasets. An ellipsoid was interactively fitted to the individual brain with an MPR program on axial, coronal and sagittal slices (this method is described in detail in [19,20]). For each point a vector was calculated extending from the center of the brain (between the bottom and the roof of the fourth ventri-

cle) to the surface of the ellipsoid. Intensity values of the anatomic and functional data were averaged along these rays within a shell of 20 mm thickness located at the surface of the cortex. The mean intensity values were transferred in polar coordinates to form the resulting 2D-image. Another shell of 1 cm thickness was positioned on the scalp surface to project the capsules onto the 2D-circle. The intensity of activation (expressed by the z-values between rest and activation) and the size of activation clusters around the central gyrus (number of activated voxels) were evaluated using SPM. Activation maxima (AM) were assessed as the highest activated voxel in the precentral gyrus. Distances from the crossing of interhemispheric fissure with the central sulcus and the activation maxima in the precentral gyrus were measured using the Euclidian distance along the surface of the selected ellipsoid. These distances were expressed as length of the precentral gyrus in percent. To this end, the total length of precentral gyrus from the central crossing point (CZ) 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 of the precentral gyrus in the control subjects (104.2 mm, $n = 10$, standard deviation (SD) = 5.4 mm) approximates the length of normalized precentral gyrus (100 mm). The relative length in % was calculated as absolute length in mm by multiplication with 1.042.

Displacements of activation maxima in patients compared to controls were defined as more than two SD ($p < 0.05$) from the average of healthy controls (see [20]).

3. Results

3.1. Clinical findings

Two patients suffered from a tumor, three from a traumatic injury causing complete SCI. The patient with incomplete SCI was diagnosed with a spinal vascular malformation. Total ASIA-score of the patients with complete SCI averaged to 110.4 and most of them showed a complete deafferentation from T7 downward. The time since the injury occurred varied considerably (mean: 829.2 weeks ranging from 6 to 1776 weeks).

3.2. fMRI

fMRI z-values and area sizes did not differ between patients and controls. For the patients with a complete SCI, the activation maxima of the BB was located significantly outside the confidence interval (average minus 2*SD) of the control subjects. This averaged about 11.9 mm into the direction of the deafferentation area (see Table 2). The location of the BB-representation maxima differed to those of healthy controls significantly $(t(9) = 5.0;\ p < 0.001)$. There was no such displacement of fMRI-activation maxima in the patient with an incomplete lesion. The location of fMRI-activation maxima of the thumb representation did not show significant differences between patients and healthy controls.

3.3. TMS

Motor thresholds did not differ between healthy controls (HC) and patients for both muscles tested. M-response amplitudes (patients: 12.85 mV; controls: 13.53 mV), latencies (patients: 4.33 ms; controls: 3.60 ms), F-wave (patients: 27.33 mV, 4.16 ms; controls: 27.38 mV, 3.48 ms) all obtained for the APB did not differ between groups ($t < 0.49$; n.s.). Repeated measurements GLM for the recruitment curve data revealed a main effect for facilitation $(F(1,7) = 128;\ p < 0.001)$ and for stimulus intensity $(F(1.6, 11.2) = 24.1;\ p < 0.001)$. Within subject interactions were present for facilitation*subject $(F(1,7) = 22.2;\ p < 0.005)$ and for facilitation*intensity $(F(2.2, 28) = 15.1;\ p < 0.001)$. Between subject effects were significant $(F(1,7) = 5.7;\ p < 0.05)$.

Post-hoc comparisons for the recruitment curve data revealed significant differences in healthy controls between the muscles tested (APB and BB; $p < 0.05$) but not for the patients. APB revealed a trend to differ between patients and healthy controls (HC; $p = 0.062$), BB showed no trend. Only HC showed a differential modulation of the cortex by stimulus intensity variation: difference between all other intensities to MT were significant above $p < 0.05$. This was not observed in patients; differential intensity did not result in significant differences in MEP. Facilitation was different to rest between healthy controls and patients for almost all stimulus intensities tested ($p < 0.05$). Differences between patients and HC were only significant for the facilitated movement ($p < 0.05$) but not for the resting condition.

Table 2
fMRI and TMS -results of patients with complete and incomplete SCI and controls

SCI	complete	complete	complete	complete	complete		incomplete	controls
Patients	1	2	3	4	5	Mean (SD)	6	Mean (SD)
fMRI APB[1]	45.0	48.8	54.2	37.8	52.4	47.6 (6.5)	51.1	46.2 (6.8)
fMRI BB[1]	34.0	29.4	33.9	29.5	15.6	28.5* (7.6)	42.6	47.2 (3.4)
TMS MT[2] APB	60	85	50	70	64	65.8 (11.6)	75	59.4 (10.9)
TMS MT[2] BB	67	95	60	100	78	80.2 (15.7)	100	84.0 (13.5)
z-value[3] APB	4.6	4.6	6.0	5.8	5.8	5.4 (0.6)	5.8	4.0 (0.9)
z-value[3] BB	4.8	3.0	5.7	3.1	6.7	4.7 (1.5)	3.7	4.9 (1.1)
fMRI voxel[4] APB	2484	734	3336	2058	2910	2304.4 (893.3)	2504	2400.8 (1833)
fMRI voxel[4] BB	726	113	475	183	7726	1844.6 (2948)	237	2401.0 (2050)

[1]Distances of fMRI-activation maxima (AM) during movement of target muscle to Cz (central crossing point) [mm]. SCI = spinal cord injury; APB = abductor pollicis brevis muscle or thumb movement; BB = biceps brachii muscle or elbow movement.
[2]Resting motor threshold of the APB and the BB as evaluated with TMS.
[3]Intensity of fMRI-activation provided in z-values for APB and BB.
[4]Activated voxels in the contralateral pre- and postcentral gyrus for the thumb and elbow movement.
*Difference patients to controls $p < 0.005$.

Silent periods revealed a main effect for muscle tested ($F(1,1) = 167.4;\ p < 0.001$). Between subject effects were significant ($F(1,7) = 59.2;\ p < 0.001$). Post hoc tests revealed differential silent periods only for the APB between patients and controls ($p < 0.005$). The BB-values showed a low statistical power since only three measurements were possible in the patients group). Nevertheless, silent periods of both muscles differed in both groups ($p < 0.001$). Patients showed prolonged silent periods for all intensities evaluated ($p < 0.001$).

3.4. Correlation of clinical data, fMRI and TMS

During both the thumb and elbow movement fMRI-intensity and activated voxels correlated as expected (over patients and controls: thumb: $r(12) = 0.74;\ p < 0.005$; elbow: $r = 0.64;\ p < 0.05$). In SCI patients resting motor threshold was negatively correlated with fMRI z-value during elbow movement ($r(6) = -0.75;\ p < 0.05$); an therefore increased excitability of the BB was associated with increased fMRI-activation during elbow movement. A comparable correlation was observed for the number of activated voxels during the APB movement and the APB resting motor threshold ($r(6) = -0.88;\ p = 0.01$). FMRI-AM displacement for the elbow movement correlated significantly with the time since the lesion was present ($r(6) = 0.84;\ p < 0.05$). This displacement correlated with activated voxels during biceps movement ($r(6) = 0.85;\ p < 0.05$); therefore, displacement was associated with an enlargement of representation area size.

4. Discussion

In this study we investigated fMRI and TMS variables in five patients with a complete SCI in the level of T3-11 and one patient with an incomplete spinal cord injury at the level of L1. Biceps fMRI-representation maxima were displaced only in patients who suffered from a complete spinal cord injury but not in the patient with incomplete SCI (see also [4] for preliminary data). APB-representation site was not displaced significantly as identified by fMRI, although its spinal motor neuron pool is located closer to the spinal lesion site.

4.1. Reorganization parameters – correlates to clinical data?

Mikulis et al. [5], who investigated tongue and upper limb representations with fMRI in 11 cervical SCI patients with different severity of lesion, reported a displacement of about 12 mm of the tongue movement into the direction of the upper limb representation adjacent to the deafferented area, but no increase in activation volume. Both findings are consistent with our observations.

Corbetta et al. [3] described an initially tetraplegic patient with an incomplete SCI at the level of C2 who showed a displacement but also an enlargement of the tongue representation into the hand area. This patient was investigated more than 7 years after severe SCI. For five years motor and somatosensory functions were almost completely absent, but a more intensive physical therapy including electrical stimulation of leg muscles resulted in self-initiated small movements of upper and lower extremities and strong somatosensory sensations. Therefore, this patient had experienced an

almost complete deafferentation of the body caudal to the neck more than 5 years, and the reorganization of the tongue might therefore parallel those observed by us and others in patients with complete SCI. Late occurrence of somatosensory sensations enabled a mapping of the hand representation with vibrotactile stimulation, which revealed a normal representation site. This anecdotic report of a rare patient with extremely late recovery does not offer a possibility to differentiate between training induced and SCI dependent reorganization processes. Additionally it cannot be differentiated between reorganization specific mechanisms of complete or incomplete injury.

The observation that a long lasting almost complete deafferentation results in displacements of other representations in the direction to the deafferented area seems to be congruent with those of us. In our study the amount of displacement of the BB correlated positively with the size of the representation area. Although the absolute number of activated voxels was not different to HC, these data might underline reports of others of an enlarged representation area of movements adjacent to the deafferented region [1–3].

Curt et al. [2] observed no enlargement of representation areas of wrist, elbow and tongue movements in comparison to healthy controls, which is congruent to findings of us and others [5]. Contrarily, they observed an increased representation area for finger movements, innervated near to the spinal lesion level. Since fingers are not located near the cortical deafferentation area, their findings are also incongruent with TMS-investigations on complete SCI [7,19].

The amount of displacement of representation sites of muscles innervated superior to the level of SCI seems to be related to the time since the deafferentation persists and the preservation of somatosensory input or motor output. This conclusion can be drawn from correlates of our study (time of SCI with reorganization of BB) and of others ([1,5]; severity of injury with tongue displacement; level of SCI with displacement). Two patients of our study, who experienced a complete SCI after malformation (patient 1 and 3) and were investigated shortly after SCI (6 and 12 weeks), showed only a small amount of displacement of the BB. Both patients experienced a sudden onset of complete deafferentation due to surgical intervention, and a long lasting adaptation to a progressing injury in contrast to traumatic SCI was not possible.

A positive correlation between the time since the SCI persisted and the displacement of representation sites near the deafferented region in M1 and the primary somatosensory cortex (S1) was also present in patients who suffered from upper limb deafferentation [20]. In amputees, an enlargement of representation area is associated with displacement of activation maxima [21], a finding also observed in the present study.

4.2. Methodological influences

It has to be kept in mind that the investigation of possible displacement of representation sites in amputees is much more precise, since the deafferented side can be compared with the intact side within the same patient. Investigations in SCI patients have to be performed with confidence intervals of movement representations of age matched healthy controls. Additionally, differences in movement parameters if patients are compared with controls cannot be completely ruled out although more proximal limbs have been fixated (for instance shoulder movements during movements of the elbow). Furthermore, differences in training of the SCI-patients in comparison to healthy controls might also result in differential reorganization of shoulder and arm muscles. This could for instance be due to the usage of wheel chairs or crutches.

Curt et al. [2] did not observe any cortical displacements of finger, wrist, elbow and tongue movements from 4 to 106 month in a quite homogenic group of nine patients after complete lumbar cord (L2–L4) lesions. Since they transformed their data into the Talairach system, it is conceivable that this procedure might distort individual activation maps and might make an accurate evaluation of representation sites impossible. In order to test this hypothesis we additionally performed a normalization of our data of elbow representation into the MNI-space. A non-linear normalization performed by SPM is different to the linear Talairach normalization used in the investigation of Curt et al., but in order to test dislocations of representation sites both methods are hampered by an unsystematic distortion. After MNI-normalization representation maxima of elbow movement in our patients were not remarkably dislocated from coordinates of HC. We therefore strongly suggest to avoid using a conventional normalization method if representation sites in patients are compared with those of HC. However, we have to admit that group comparison between SCI patients and HC always comprises some kind of a normalization process, since a direct comparison with an unaffected hemisphere – as performed in amputees – is not possible.

4.3. Conclusion of the imaging results

In conclusion, most fMRI and PET- findings in patients after a complete SCI point to a displacement of movements more cranial to the SCI level, but are inconsistent in regard to an enlargement of the representation area. It seems to be that an enlargement is observed in relation to the displacement and this might predominantly involve movement representations near the deafferented region. Additionally, displacements correlate with clinical and demographic findings such as the level of injury, the severity of injury (in incomplete SCI) and the time a complete SCI is present. Incongruent results might be predominantly caused by different evaluation techniques used and the small number of patients investigated.

4.4. TMS results – comparison to other studies

In incomplete SCI, TMS is a method to investigate the integrity of cortico-spinal connections [23]. In muscles, innervated by roots caudal to an incomplete SCI, increased conduction latencies [24] and TMS thresholds may reflect degraded corticospinal transmission in the spinal cord [25]. Our study, centered on plasticity processes of muscles cranial to the spinal injury after complete SCI, demonstrated different recruitment curves of patients and HC. The APB, supplied by motor neurons that are located more distinct from the cortical deafferented area than BB, showed decreased cortical excitability. Additionally, other observations, such as a lack of relevant increase of MEP amplitudes with increasing stimulus intensities and prolonged silent periods after SCI, point to a reduced excitability of the cortical areas inferior-lateral to the deafferented area. This data are partially consistent with a study using TMS in 13 complete and incomplete SCI patients (thoracic and lumbar level [8]), who described a decreased facilitative effect on MEPs of the BB. An increased excitability of abdominal wall muscles in 8 patients with complete thoracic SCI [7] point to an effect which is dependent on the distance to the deafferented area. It could be conceivable that thoracic representations near the deafferented area are increased in excitability. This might be due to a lack of lateral inhibition caused by the deafferented region. An increased excitability around the deafferentation site increases lateral inhibition on more distal representation areas differentially expressed in relation to the level and severity of injury. This might cause a decreased facilitation as observed in the BB in the study of Laubis-Herrmann et al., and the APB in our patients.

4.5. Mechanisms underlying reorganization as detected by TMS

By controlling the M-response and the F-wave for the APB we demonstrated that spinal mechanisms can not explain changes in excitability observed after complete SCI. This is in line with observations of others [7] and these changes are therefore likely to be caused by excitability changes in the cerebral cortex. Whereas the RC-changes are dependent on several neurotransmitters such as dopamine, GABA and norepinephrine, the cortical silent period refers to a TMS induced interruption of voluntary activity in the EMG of the target muscle [26]. While spinal inhibition contributes to the early part of the SP, the late part originates most likely in the motor cortex and especially to GABA B receptors [27]. Taken together, the observations of differences in RC and SP suggest that changes of the GABAergic system might be crucially involved in the plastic changes observed in SCI patients. Nevertheless, these suggestions have to be investigated in detail with a paired pulse technique which is more sensitive to cortical inhibitory or facilatory effects [28].

4.6. Combination of fMRI and TMS – new insights?

A combination of both methods have to be interpreted with care since the motor performance during fMRI is quite different to the muscle twitch elicited with TMS. Nevertheless we observed parallels of fMRI and TMS parameters which are interesting and might be related to the same changes in cortical excitability.

4.6.1. Correlates between fMRI and TMS

In our patient group we observed a correlation between the motor thresholds of the BB, but also the APB and the fMRI-parameters for BOLD-intensity (highest z-value, number of activated voxels). The lower the TMS-resting threshold, the higher the fMRI-activation intensity. This result underlines reports of correlates of cortical excitability and fMRI-effect intensity during motor tasks in the primary motor cortex in HC [29]. Additionally it relates findings about increased excitability (TMS) and an increased representation volume (fMRI) for movement represented adjacent to the deafferented area.

4.6.2. Comparison of findings in SCI-patients and those observed after peripheral lesions

It could be helpful to compare results obtained after SCI with results reported after complete peripheral deafferentation – a pathology where more precise observations could be obtained.

After complete peripheral nerve lesion – such as upper limb amputation – enlarged M1-representation sites, increased MEPs and a larger percentage of motor neuron pool activation compared to those of the intact side were reported for cortical stump representations contralateral to the amputated arm by using TMS [30, 31]. Increased excitability observed in upper limb amputees might be related to painful phantom limb sensations [32] frequently seen after limb amputation. Additionally, cortical excitability might be increased if the movement is associated with an increased attentional demand due to disability or pain. An interaction between attention and sensorimotor integration resulting in an increase of motor cortex excitability has been reported recently [33]. These cortical changes can not be explained by changes in the spinal level [30]. Therefore, the increase of cortical excitability, a common finding in pain patients [34], probably modulates cortical reorganization in patients with phantom limb pain.

SCI patients do not experience comparable painful phantom limb sensations, although non-painful phantom sensations have been reported [35] which go along with cortical reorganization in the postcentral gyrus [36]. The persistence of deafferentation for a longer period of time results in an increase of cortical displacement of representation sites pointing to a long-lasting progressive development. Considering the large magnitude of reorganization in our patients spanning on average a distance of 18.7 mm, cortical sprouting is implausible. Similar to the processes seen in amputees an unmasking of horizontal connections by decreases of GABA-related inhibition might probably regulate the strength of excitatory horizontal connections through feedforward inhibition [37,38].

Additionally, it has to be kept in mind that movements are not only muscle twitches and are operated by functional loops of neurons which are represented in different areas of the precentral gyrus and are dependent on somatosensory feedback. Therefore, altered representation sites could well be due to altered centers of neuronal networks present already without deafferentation.

If cortical mechanisms are the cause of massive reorganization, it might most reasonably not be modulated by anatomical changes of the cortical grey and white matter, since these structures do not differ from HC [39], but are most likely due to new patterns in the neuronal connectivity. Additionally, reorganization within structures up-stream of the cortex such as the caudate nucleus [40] might contribute to cortical changes.

5. Conclusion

We assume that divergent results observed with different methods in representation sites cranial to a complete SCI might be due to different distances of the representation sites to the deafferented area. For very adjacent representations an increase of excitability has been observed, similar to observations in amputees. Since in amputation phantom limb pain enhances excitability, the area with increased excitability is larger than those in SCI patients. In SCI patients the area with increased excitability is probably neighbored by another region with decreased excitability. However, also representation sites located in this region are substantially displaced in comparison to HC. Changes in excitability might be predominantly associated with GABAergic processes a suggestion which has to be addressed in future studies in detail.

The combination of fMRI and TMS provides additional information about altered cortical processes after complete SCI. Nevertheless, many questions could not be answered with this approach. Future studies should investigate representation sites and excitability in a more detailed procedure and a larger number of patients. Additionally, the question of changes in excitability over time should be addressed. Furthermore, the effect of training of the muscles represented nearby the deafferented site might be investigated in patients suffering from complete SCI in a follow-up study for instance in those patients who underwent specific motor training for instance in sports involving especially the upper arm and shoulder muscles.

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