

## SHORT COMMUNICATION

# How does the human brain deal with a spinal cord injury?

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### Abstract

The primary sensorimotor cortex of the adult brain is capable of significant reorganization of topographic maps after deafferentation and de-efferentation. Here we show that patients with spinal cord injury exhibit extensive changes in the activation of cortical and subcortical brain areas during hand movements, irrespective of normal (paraplegic) or impaired (tetraplegic patients) hand function. Positron emission tomography (<sup>15</sup>O]-H<sub>2</sub>O-PET) revealed not only an expansion of the cortical 'hand area' towards the cortical 'leg area', but also an enhanced bilateral activation of the thalamus and cerebellum. The areas of the brain which were activated were qualitatively the same in both paraplegic and tetraplegic patients, but differed quantitatively as a function of the level of their spinal cord injury. We postulate that the changes in brain activation following spinal cord injury may reflect an adaptation of hand movement to a new body reference scheme secondary to a reduced and altered spino-thalamic and spino-cerebellar input.

### Introduction

Somatotopic plasticity of the sensorimotor cortex following partial disconnection from the body has been shown in animal experiments (Calford & Tweedale, 1988; Byrne & Calford, 1991; Pons *et al.*, 1991; Florence *et al.*, 1996) and in man (Flor *et al.*, 1995). Transcranial magnetic stimulation (TMS) has revealed cortical reorganization in adult humans, e.g. in amputees (Cohen *et al.*, 1991; Kew *et al.*, 1994), after nerve root avulsion with upper limb paralysis (Mano *et al.*, 1995), during peripheral nerve blockade (Brasil Neto *et al.*, 1992) and after spinal cord injury (SCI) (Levy *et al.*, 1990; Topka *et al.*, 1991; Streletz *et al.*, 1995). Under resting conditions, SCI patients showed a relatively increased glucose metabolism in brain regions involved in attention and movement initiation (Roelcke *et al.*, 1997).

Patients with SCI provide a human model in which the effects of de-afferentation and de-efferentation on brain centre activation can be studied. Such changes can be correlated with the level of spinal lesion (and by inference the amount of the body that is 'isolated' from the brain). The aim of this study was to evaluate changes of functional brain activity in patients following SCI; activity was measured during hand movements and compared with that measured in healthy control subjects. We hypothesized an expansion of the cortical hand area, depending upon the degree of intact motor function following SCI at different spinal levels.

### Methods

#### Subject groups

The study was approved by the Ethics Committee of the University Hospital Balgrist and performed with the informed consent of the

patients and the healthy subjects. Both paraplegic and tetraplegic patients were included in this study. No patient had suffered a head or brain lesion associated with the trauma leading to the SCI. The post-traumatic Glasgow Coma Scale of all patients was normal.

The paraplegic group consisted of four males and three females (mean age 32 years; range 23–40 years). The mean period following SCI in these patients was 2.9 years (range 0.3–9.9 years). The levels of SCI were thoracic (T2, T4, T6, T11, T12, T12) or lumbar (L1). All paraplegic patients displayed normal hand function.

The tetraplegic group consisted of seven males with a mean age of 26 years (range 18–46 years). The mean time post-trauma was 4.7 years (range 0.5–8.5 years). The levels of spinal lesion were cervical (C5, C5, C5, C5, C5, C6 and C7). All paraplegic and tetraplegic patients were assessed according to the American Spinal Injury Association protocol. The mean upper limb motor score for the right hand in all tetraplegic patients was 10 out of a possible 25 points (range 1–21 points). Thus, although the hand function of all tetraplegic patients was impaired (loss of intrinsic hand function) they could all perform the required motor task.

Control subjects were all male, with a mean age of 27 years (range 24–32 years).

#### Experimental protocol

We used positron emission tomography [<sup>15</sup>O]-H<sub>2</sub>O-PET to measure regional cerebral blood flow (rCBF) as a correlate for neuronal activity (Grafton *et al.*, 1991). Brain images were obtained with a General Electric Advance PET scanner in the 3-D acquisition mode. Plasma radioactivity during the scans was not measured. Although

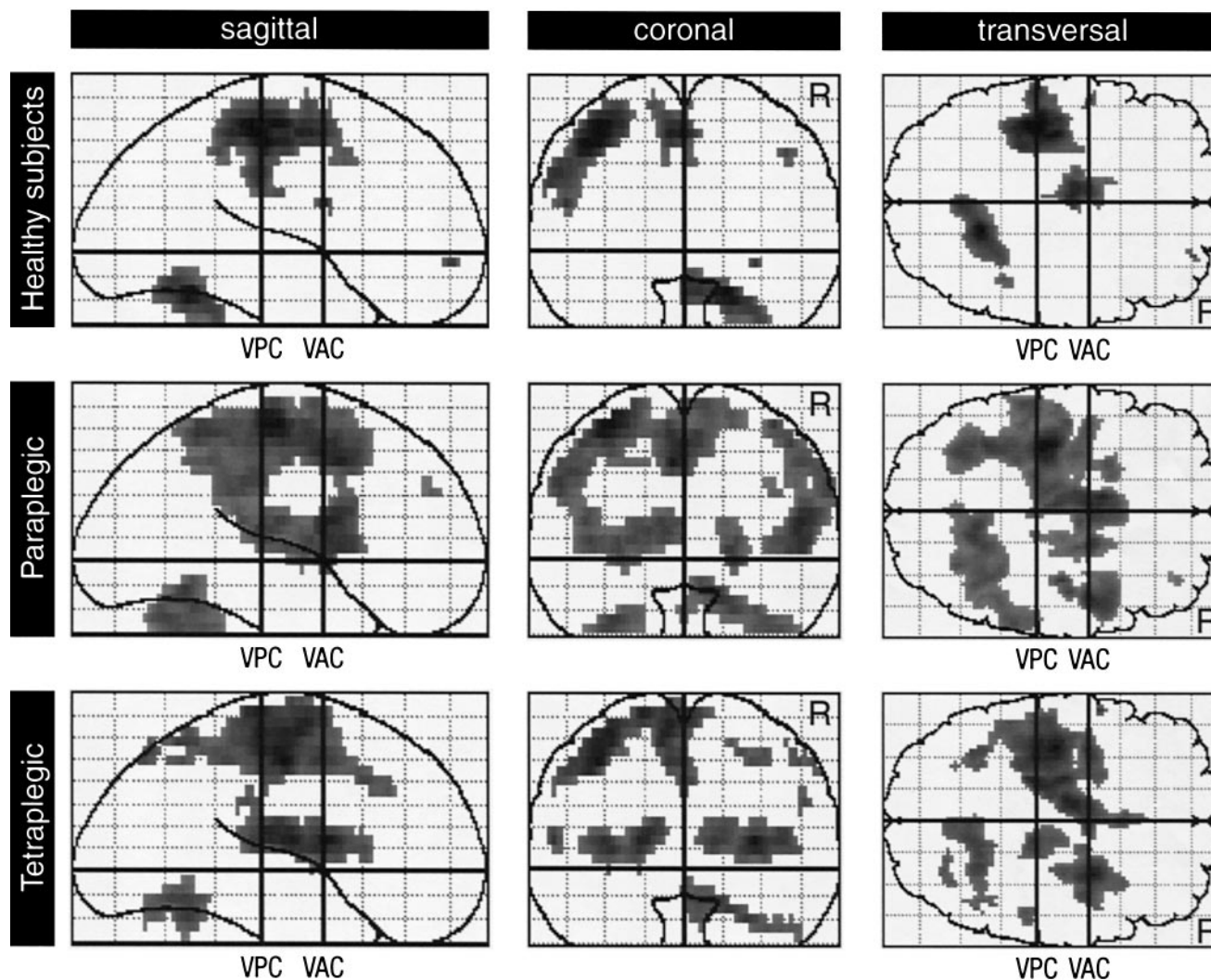


FIG. 1. Brain activation in healthy, and paraplegic and tetraplegic subjects. Differences in rCBF between resting and joystick-movement conditions of the right hand in eight healthy subjects, seven paraplegic and seven tetraplegic patients. Brain areas showing a significant activation (i.e. increased rCBF during joystick movements,  $P < 0.0001$ ) are displayed in three projections (sagittal, coronal and transverse) by SPM (Friston *et al.*, 1991). VPC, vertical posterior commissural line; VAC, vertical anterior commissural line.

this technique does not allow the calculation of the absolute CBF, changes in rCBF relative to a global mean can be detected.

Brain activation was assessed during repetitive joystick movements of the right hand. Subjects were instructed to choose, at random, one of four possible movements (forward, backward, right or left), in order to avoid repetition of one movement direction more than three times during one scanning session. Joystick movements were externally triggered at a frequency of 40 beats per minute, using a metronome as an auditory cue. The metronome was beating during all scans (including those without movements) in order to separate the effects of the auditory input. The performance of the motor task was controlled visually by the investigator. No differences were noted between the joystick movements of healthy control subjects and paraplegic patients. Tetraplegic patients had difficulties in feeling and holding the joystick grip, and there was an involuntary component of radial hand movement adduction. However, all tetraplegic patients were able to move the joystick into all four directions at the required frequency. Motor activation and rest conditions were scanned twice. One minute prior to intravenous injection of 500–600 MBq [ $^{15}\text{O}$ ]- $\text{H}_2\text{O}$ , the patients were instructed to close their eyes and to start

moving the joystick. The scanning was started when the radioactivity of the head exceeded 50 000 counts per second (indicating the arrival of the tracer bolus in the brain). The scan duration was 90 s. To allow sufficient decay of resting radioactivity, the scanning was repeated after 12 min. Images were reconstructed, controlled for alignment, transformed into stereotactic space (Talairach & Tournoux, 1988) and smoothed using a Gaussian filter (10 mm full width half maximum). After normalization of the images, statistic parametric mapping (SPM) between resting and movement conditions was performed for all groups using SPM95 software (Friston *et al.*, 1991) on a SPARC station 2.

## Results

Figure 1 shows those brain areas activated by repetitive joystick movements in paraplegic and tetraplegic patients, and healthy subjects. A previous study has shown that in healthy subjects a motor task similar to that used in this study resulted in activation of the contralateral sensorimotor cortex (SMC), supplementary motor area (SMA) and premotor cortex and a bilateral activation of the superior

TABLE 1. Performance-induced increases in rCBF in different subject groups. Table showing those regions of the brain where a significant increase ( $P < 0.0001$ ) in rCBF was measured in each subject group. Values are expressed as percentage increases in rCBF between the resting and joystick-movement conditions. Maximum activation of the SMC was close to the central sulcus and extended to both the pre- and postcentral gyrus (primary motor and sensory cortices, respectively). In healthy subjects, no significant increase in rCBF was observed in those brain regions which are listed in the patient groups, but not in the control group

Group	Region	Side	rCBF increase (%)
Control	SMC	Contralateral	18.3
	SMA	Contralateral	15.6
Paraplegic	Cerebellum	Ipsilateral	10.5
	SMC	Contralateral	20.6
	SMA	Ipsilateral	15.3
	Thalamus	Contralateral	9.9
	Thalamus	Ipsilateral	9.7
	Putamen	Contralateral	7.0
	Putamen	Ipsilateral	8.9
	SMC	Ipsilateral	9.6
	Pallidum	Ipsilateral	8.9
	Cerebellum	Ipsilateral	12.1
	Cerebellum	Contralateral	8.7
	Parietal	Ipsilateral	10.0
	Tetraplegic	SMC	Contralateral
SMA		Contralateral	13.2
Thalamus		Contralateral	11.7
Thalamus		Ipsilateral	10.1
Putamen		Ipsilateral	11.8
Insula		Contralateral	9.6
Cerebellum		Ipsilateral	11.1
Parietal		Ipsilateral	10.7

parietal cortex (Deiber *et al.*, 1991). Although our control subjects also demonstrated a significant increase in rCBF ( $P < 0.0001$ ) in the contralateral SMC, under our experimental conditions, a bilateral increase in the SMA and an ipsilateral increase in the cerebellum were observed.

In paraplegic and tetraplegic patients, the pattern of brain activation was strikingly different from healthy subjects (Fig. 1, Table 1). In both patient groups, more of the contralateral SMC and SMA, and ipsilateral cerebellum was activated. In addition, there was bilateral activation of the thalamus and parts of the basal ganglia and, in paraplegic patients, of the contralateral cerebellum and the ipsilateral SMC. Since identical thresholds ( $P < 0.0001$ ) were used for SPM images from all groups (tetraplegic, paraplegic and healthy control subjects; see Fig. 1) and group sizes were similar, the differences of brain activation between groups are unlikely to be due to threshold effects. Furthermore, the significance of additional activation in paraplegic and tetraplegic patients was confirmed by direct categorical SPM comparisons between each patient group and the control group ( $P < 0.001$ ). Figure 2 shows that the degree of activity in these brain areas was related ( $P < 0.001$ ) to the level of the SCI, i.e. rCBF during motor activation was significantly positively correlated with the number of neurally 'disconnected body segments'.

## Discussion

The most important observations in the patient groups were as follows. (i) Within the SMC, activation of the cortical 'leg area' was observed in addition to the normally activated cortical 'hand area'. An increased activation was also observed in the thalamus and cerebellum. (ii) This enhanced activation of brain centres was not related to hand function. (iii) There was a quantitative relationship

between abnormal brain activation and the number of 'disconnected body segments' (i.e. the number of spinal segments below the lesion site). An expansion of the cortical area was not unexpected, as it has previously been demonstrated with TMS (see above). However, the other observations are novel, and to our knowledge they have not yet been described.

The strong additional activation of the thalamus and cerebellum in patients with SCI suggests that a basic reorganization of neuronal activity occurs within these supraspinal sensorimotor centres, most probably as a consequence of a reduced and altered afferent input from the spinal cord. These changes are not directly related to performance of the requested hand movement, as the additional activation of brain nuclei was also present in the paraplegic patients who retained normal hand function. In this context, one has to consider that any voluntary hand movement is performed in relation to the body, which serves as a reference. In addition, any limb movement must be associated with an appropriate compensatory reaction of the body (Hess, 1965). Consequently, body adjustments will be scaled depending on the magnitude of the voluntary hand movement. In paraplegic patients, where part of the body is neurally isolated from the brain, it can be assumed that the new relationship between hand movement and feedback from the body is being recalibrated and remapped.

Both the thalamus and cerebellum are known to process afferent input from the spinal cord (Brooks, 1981). In addition, the thalamus also serves as a relay nucleus to the motor cortex with internal loops from the basal ganglia and the cerebellum, thus matching corticospinal output with spino-cerebellar afferent input (Alexander *et al.*, 1986). We assume that by reducing afferent input from the spinal cord, a more complex processing of the remaining input leads to stronger activation, or possibly to disinhibition, of the neuronal centres involved, i.e. the thalamus and cerebellum. It is also possible that the bilateral cortical changes may be secondary effects mediated by thalamic and cerebellar inputs. These changes are necessary in order to allow 'normal' hand movements in paraplegic patients with respect to the altered body-state. The judgement of normal joystick movement by the paraplegic patients was based on visual control only. Nevertheless, a detailed analysis in these patients of hand movement with respect to body reaction might reveal subtle motor pattern abnormalities which are not visually obvious.

Surprisingly, paraplegic patients showed a stronger and more widespread cortical activation compared with tetraplegic patients. This may be explained by the impaired sensorimotor hand function in many tetraplegic patients with a support of joystick movements by proximal arm muscles. Nevertheless, in both paraplegic and tetraplegic patients, the strength of activation correlated with the number of spinal segments disconnected by the SCI, in all brain areas with abnormal additional activation (see Fig. 2). This correlation was mainly based on results from paraplegic patients, since there was a larger range of SCI levels in paraplegic than in tetraplegic patients. Therefore, a similar correlation was obtained, when only the PET images of paraplegic patients (with normal hand function) were taken for calculation. Consequently, the size of the neurally 'disconnected body' can be considered as the main variable determining the strength of abnormal brain activation. Thus, the higher the level of spinal lesion the stronger the adaptational processes for any remaining input from the spinal cord. It is suggested that this provides the ability to perform voluntary hand movements with respect to the new body reference scheme.

Our observations increase the understanding of supraspinal sensorimotor systems responding to neuronal disconnection of a part of the body. This may be of importance for rehabilitative purposes.

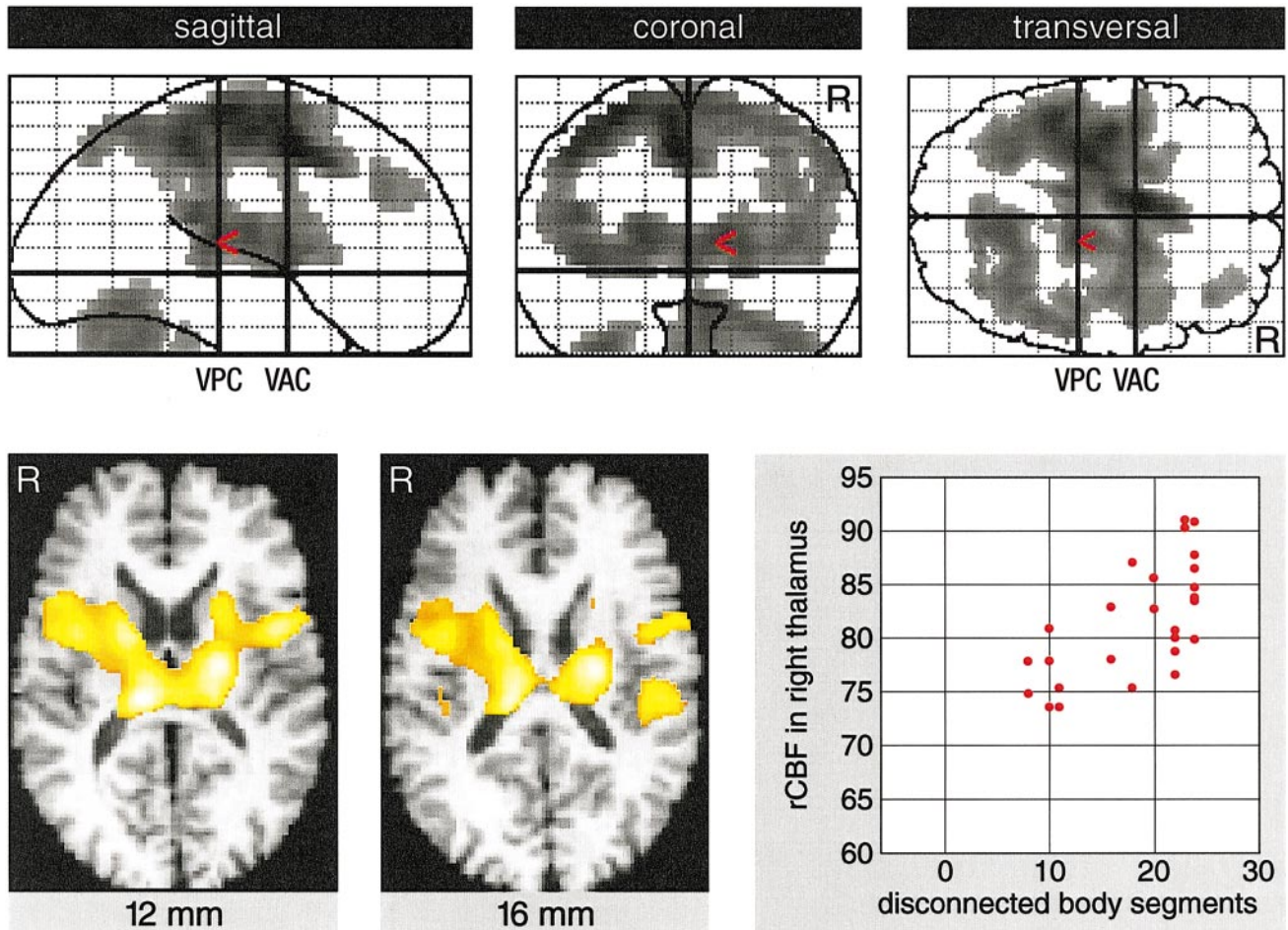


FIG. 2. Strength of brain activation and level of lesion. *Upper panel*: Activated brain regions showing a positive correlation between the strength of activation during joystick movements of the right hand and the number of 'disconnected body segments' by SCI from all patients (28 scans from two joystick activation conditions from each patient). All spinal segments distal to the lesion were considered (e.g. SCI at thoracic level T10 gave a total of 12 'disconnected segments': 2 thoracic (11 and 12), 5 lumbar and 5 sacral). All activated areas (i.e. the SMC, SMA, thalamus, basal ganglia, insula and cerebellum) showed a positive correlation ( $P < 0.001$ ). *Lower panel, right side* shows an example from one area: correlation between the level of the spinal lesion (expressed as the number of disconnected body segments/vertebrae) and relative rCBF (arbitrary units) in the right thalamus (red arrow in the upper panel) during joystick movements. *Lower panel, left side* shows two image planes through the thalamus and the basal ganglia, at a height of 12 and 16 mm above the zero plane in the coordinate system (Talairach & Tournoux, 1988), each superimposed on a standard MRI. Areas showing a positive correlation are coloured.

It is evident that, even with apparently normal motor function, cerebral adaptations to SCI have occurred.

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### Abbreviations

PET	positron emission tomography
rCBF	regional cerebral blood flow
SCI	spinal cord injury
SMA	supplementary motor area
SMC	sensorimotor cortex
SPM	statistic parametric mapping

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