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Brain motor system function after chronic, complete spinal cord injury

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Most therapies under development to restore motor function after spinal cord injury (SCI) assume intact brain motor functions. To examine this assumption, 12 patients with chronic, complete SCI and 12 controls underwent functional MRI during attempted, and during imagined, right foot movement, each at two force levels. In patients with SCI, many features of normal motor system function were preserved, however, several departures from normal were apparent: (i) volume of activation was generally much reduced, e.g. 4–8% of normal in primary sensorimotor cortex, in the setting of twice normal variance in signal change; (ii) abnormal activation patterns were present, e.g. increased pallido–thalamocortical loop activity during attempted movement and abnormal processing in primary sensorimotor cortex during imagined movement; and (iii) modulation of function with change in task or in force level did not conform to patterns seen in controls, e.g. in controls, attempted movement activated more than imagined movement did within left primary sensorimotor cortex and right dorsal cerebellum, while imagined movement activated more than attempted movement did in dorsolateral prefrontal cortex and right precentral gyrus. These modulations were absent in patients with SCI. Many features of brain motor system function during foot movement persist after chronic complete SCI. However, substantial derangements of brain activation, poor modulation of function with change in task demands and emergence of pathological brain events were present in patients. Because brain function is central to voluntary movement, interventions that aim to improve motor function after chronic SCI likely also need to attend to these abnormalities of brain function.

Keywords: motor system; spinal cord injury; plasticity

Abbreviations: DLPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; SCI = spinal cord injury; STG = superior temporal gyrus; SMA = supplementary motor area

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Introduction

Spinal cord injury (SCI) remains a major source of disability. A number of therapies are being developed to restore motor function in this population. Some focus on SCI repair (Dobkin and Havton, 2004). Others aim to drive muscles or devices with signals derived from cortical recordings (Carmena *et al.*, 2003; Friehs *et al.*, 2004). Both approaches are predicated upon the assumption that brain motor functions remain capable of generating signals needed to drive limb movement, but this issue has received limited study after SCI.

Single limb movements, and the afferent signals they generate, are normally associated with activation of primary motor cortex plus a broad sensorimotor network. Electrophysiological studies suggest that sensorimotor cortex function in a healthy brain becomes disorganized after years of plegic SCI. Though subcortical processing remains intact chronically after SCI (Ament *et al.*, 1995), amplitude and latency of movement-related potentials recorded over primary motor cortex are reduced, and variance in these measures is twice normal (Green *et al.*, 1999; Lacourse *et al.*, 1999). Previous functional neuroimaging studies of SCI effects on the motor system have provided conflicting results (Sabbah *et al.*, 2002; Alkadhi *et al.*, 2005). Based on studies of patients with chronic hemiplegic stroke (Cramer *et al.*, 2002*a*), the primary aim of the current study was to test the hypothesis that chronic complete SCI is associated with reduced volume

of motor network focal activation peaks. The chronic form of SCI was studied because this represents the strongest expression of SCI effects on brain function, and because of the high prevalence, and therefore therapeutic importance, of patients with chronic SCI.

Motor output is not a static event but instead requires modulation during performance of most tasks. In consideration of this, the effect of chronic SCI on modulation of brain motor function was also evaluated, in two different ways. First, the motor task was modulated by contrasting attempted movement with imagined movement. Attempted movement is of interest because of its direct relevance to therapeutic goals, while imagined movement is of interest because it better matches motor output between subject groups. Imagined movement, as compared with attempted movement, normally has extensive overlap in activation sites (Grezes and Decety, 2001) but reduced activation magnitude (Porro *et al.*, 1996; Grezes and Decety, 2001). This normal task-dependent change in brain activation was hypothesized to be preserved after SCI. Second, force output level was modulated. Many brain areas normally show increased activity across a wide range of forces (Dettmers *et al.*, 1995; Kuhtz-Buschbeck *et al.*, 2001; Cramer *et al.*, 2002*b*). For imagined and attempted movement, modulation of motor system function with increased foot force was hypothesized to be present in controls and preserved in patients with SCI.

Materials and methods

Subjects

Twelve patients with SCI and twelve healthy, age-matched controls signed consent forms and were enrolled. The entry criteria were age 18–80 years and no contraindication to MRI scanning. Controls were required to be right-footed (Coren, 1993) and to have no major neurological disease. Patients were required to have SCI >1 year prior, complete sensorimotor deficits at T6 or higher level including classification as Grade A on the ASIA Impairment Scale and no other neurological disease including no traumatic brain injury. Institutional Review Boards at Veterans Affairs Healthcare System, Long Beach, and California State University, Long Beach approved this study.

Selection of foot motor tasks

Our goal was to present fMRI subjects with images of foot movements requiring either a low or a high force level. To classify foot movements in this manner, 25 different video clips of 3 s duration were produced each showing a right foot hovering above an object, then moving in plantarflexion to crush the object. A group of 53 undergraduate students was asked to rate the force level required to crush each object using a visual analogue scale. Ten video clips, five showing highest-rated and five showing lowest-rated force levels, were retained for fMRI studies.

Behaviour and EMG assessments

All subjects underwent exam prior to MRI, including ASIA Motor Score plus ASIA Sensory Scores to both light touch and pin. ASIA Impairment Scale was confirmed as Grade A for patients, and normal exam was confirmed in controls. Handedness (Oldfield, 1971) and footedness (Coren, 1993) were measured. A motor imagery skill survey was adapted from Goldenberg *et al.* (1989).

Next, subjects watched four videos to prepare for the fMRI. Video 1 showed a complete foot movement—a right foot above an object, then the foot completing the movement by plantarflexing to crush the object—so that subjects would understand the task to be performed. Video 2 showed the foot above each object but with no subsequent plantarflexion. Subjects were told that they would later be asked to either imagine or attempt completion of the plantarflexion movement. Next, the actual videos used during fMRI were presented. Each alternated 30 s rest (a foot at rest, new image every 3 s) with 30 s of active state (a foot hovering above an object, with a new object every 3 s). For Video 3, instructions during active state were to imagine movement completion; for Video 4, attempt movement completion even if one's foot did not move. Unbeknownst to subjects, each 30 s active state block was either all low-force or all high-force video clips.

Surface EMG leads were affixed using bipolar leads from four muscle groups (right tibialis anterior, right quadriceps femoris, left tibialis anterior and right cervical paraspinal/medial trapezius) during this rehearsal, with subjects supine. Signal was amplified and filtered (band pass 30/2000 Hz), converted to digital data and recorded using Chart (iWorx, Dover, NH). Bilateral MRI-compatible ankle splints that went from lower tibia to toes were also placed, restricting movement to 10° of ankle dorsiflexion/plantarflexion without lateral leg rotation.

MRI acquisition

Using a 1.5 T Eclipse scanner (Marconi), a whole-brain high-resolution volumetric anatomical scan was acquired, with in-plane resolution 0.94 mm^2 and slice thickness 2.5 mm. Functional scans were acquired next, with a gradient-echo echoplanar imaging sequence, axial slices = 5 mm thick without gap, TE = 40 ms, TR = 3 s, flip angle = 90°, FOV = 24 cm and acquisition matrix 128 × 128. A total of 170 volumes were acquired for each of the two fMRI scans, with the first scan showing Video 3 and the second scan showing Video 4. Subjects wore earplugs, MRI-compatible video goggles plus the MRI-compatible ankle splints and had arms at side plus head stabilized with pads and tape.

At the conclusion of imaging, patients were asked (i) to rate 1–10 their perceived difficulty for imagining the requested right foot movements and (ii) whether they noticed that each active state block contained either all low-force or all high-force images.

Data analysis

Images were analysed using random effects methods in SPM99. For each of the two fMRI scans for each subject, the first two volumes were removed because of tissue non-saturation. Remaining images were realigned, coregistered to the volumetric scan, spatially normalized, transformed into MNI stereotaxic space and spatially smoothed (4 mm FWHM). Images at rest were contrasted with images during imagined (Scan 1) or attempted (Scan 2) right foot movement for each subject. A one-sample *t*-test was used to characterize each subject group during imagined movement and during attempted movement. Also, separate *t*-tests produced a map for the two different force levels for each group and task, from which low-high force versus high–low force contrasts were evaluated using paired *t*-tests. Paired *t*-tests were also used to contrast imagine

versus attempt for each group. A one-way ANOVA was used to contrast results between controls and patients with SCI.

One set of analyses examined the entire brain to determine the site and size of activation clusters with significantly increased activity during task performance, analysed at threshold of $P < 0.001$ without correction for multiple comparisons. Data analysis was performed separately for right and left brain, using a hemi-brain mask, because some right-brain and left-brain activation foci were fused in whole-brain analyses owing to mid-line location of foot motor areas.

To further characterize task-related fMRI changes, a second set of analyses used a threshold-independent method to measure task-related signal change within leg primary motor cortex and within leg primary sensory cortex. Task-related signal change was measured in two regions of interest, left mesial precentral gyrus (volume = 565 mm^3) and left mesial post-central gyrus (volume = 653 mm^3), each contralateral to foot movements. These two regions were drawn on the SPM single subject anatomical T1-weighted template, without knowledge of fMRI results. Task-related signal change within these two regions of interest was extracted from each subject's data using MarsBaR (Brett *et al.*, 2002).

For EMG data, the root mean square values were determined for the first 20 s of the first four rest and four active blocks, separately for each of the two tasks. For each task, values for rest cycles were averaged, as were values for active cycles. For each muscle during each task, the ratio of active: rest EMG signal was then determined. For each muscle, ANOVA testing of EMG by disease status (SCI/control) × task (imagine/attempt) × force level (low/high) was conducted separately.

Results

Subjects

Clinical features are presented in Table 1. All subjects were male. All were right-handed except for an ambidextrous patient. All were right-footed except for two ambipedal patients. Patients were 22 ± 2 (mean ± SEM) years after SCI. Level of SCI was C5 in three, C6 in two, C7 in two, T2 in one, T4 in two and T6 in one. During scanning, controls performed as instructed in all cases. Patients demonstrated no visible movements during scanning except one patient who had a few unilateral distal lower extremity spasms. One of the 12 patients with SCI demonstrated excess head movement artefact for both fMRI tasks and was excluded from further analysis.

Table 1 Clinical data

	Controls	Patients	*P*
Number (*N*)	12	11	
Age (years)	42 ± 15	47 ± 6	NS
ASIA light touch sensory score	112 ± 0	33 ± 15	<0.0001
ASIA pinprick sensory score	112 ± 0	29 ± 15	<0.0001
ASIA motor score	100 ± 0	34 ± 15	<0.0001
Percentage correct on motor imagery questions	95 ± 9	93 ± 13	NS
Percentage discerned that high and low force images presented separately	58	55	NS
Level of difficulty for imagining movements (1–10, 10 is easiest)	8.2 ± 1.2	7.6 ± 2.9	NS

Values are mean ± SD. NS = not significant.

EMG

Findings during EMG (Fig. 1) were significant for right tibialis anterior muscle for main effect of disease status [$F(1,22) = 6.43$; $P < 0.02$] and the disease status x task interaction [$F(1,22) = 6.44$; $P < 0.02$]. The interaction showed a large increase in EMG activity for the control group during attempted movement. Other EMG results were not significant.

Attempted movement

During attempted movement of the right foot, controls showed activation in a network that included bilateral primary sensorimotor cortex, supplementary motor area (SMA) and cerebellum (see Table 2 and Fig. 2). Other areas included left thalamus, right anterior cingulate and left superior temporal gyrus (STG) + sulcus. Increased age did not correlate with increased activation in any area.

In patients with SCI, activation was present in most key areas activated in controls but the volume of significant activation peaks was generally reduced (Table 2). For example, activation volume in left precentral gyrus + SMA was 8% of controls. Patients also showed activation within the

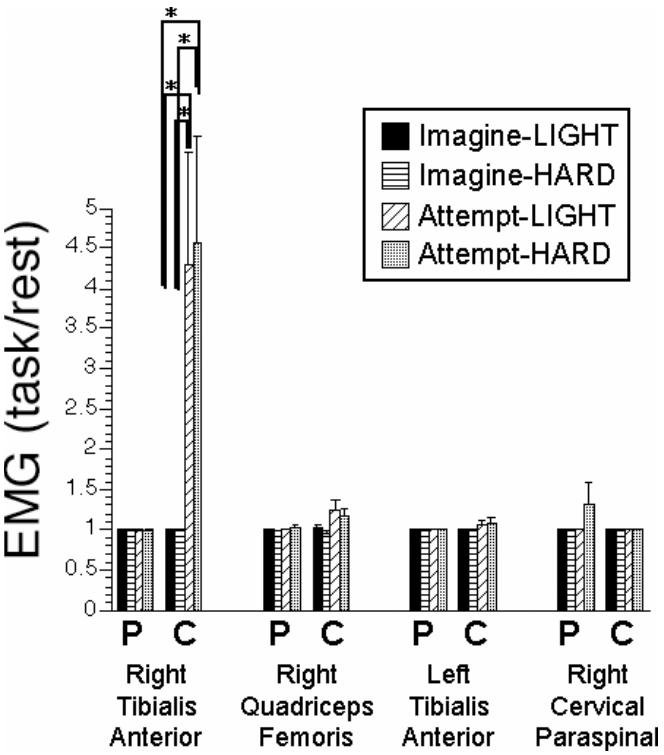

Fig. 1 EMG levels during pre-scanning rehearsal. Data are EMG during task performance, as a ratio of EMG during rest for each subject. Mean ± SEM; P = patient with SCI; C = control; *$P < 0.05$ using paired testing.

Table 2 The fMRI single group, single task results

Group	Task	Cluster size	Coordinates	Brain region	
Control	Attempt versus rest	451	−14, −42, 64	**Left**	precentral/postcentral gyri + SMA (see Fig. 2A and B)
		374	−48, −40, 48		IPL
		253	−10, −4, 44		Anterior cingulated
		159	−46, 8, −2		STG + insula
		97	−36, −58, −40		Cerebellum, declive
		34	−60, 62, 6		STG + middle temporal gyrus
		26	−20, −16, 14		Thalamus (see Fig. 2C)
		318	16, 8, 50	**Right**	anterior cingulate + medial frontal + SMA
		226	10, −52, −30		Dorsal cerebellum (see Fig. 2D)
		181	50, 8, 2		STG + ventral precentral gyrus
		97	62, −28, 20		Parietal operculum (SII)
		46	48, −30, 22		IPL/intraparietal sulcus
		36	32, 54, 0		Ventral prefrontal
		22	0, −34, 58		Medial precentral gyrus
		18	26, −44, 64		Post-central gyrus
		17	30, −64, −40		Posterior cerebellum
SCI	Attempt versus rest	69	−20, −48, −36	**Left**	anterior cerebellum
		61	−28, −8, 18		Ventral precentral gyrus + insula
		52	−22, −16, 0		Globus pallidus (see Fig. 2E)
		43	−28, −38, 14		Temporal lobe
		41	−30, −32, 36		Post-central gyrus
		36	−4, −24, 62		Precentral gyrus + SMA (see Fig. 2A and B)
		32	−40, −52, −8		Temporal lobe
		28	−40, −34, −4		STG + middle temporal gyrus
		24	−22, −20, 10		Thalamus (see Fig. 2C)
		41	14, 4, 56	**Right**	SMA
		29	28, −16, 58		Precentral gyrus + premotor cortex
		29	16, −42, −26		Dorsal cerebellum (see Fig. 2D)
		24	18, 6, 32		Anterior cingulated
		21	10, −72, −38		Cerebellum, pyramis
		20	44, 6, 12		Insula
		19	36, −42, 16		STG
Control	Imagine versus rest	748	−58, 6, 12	**Left**	insula and ventral precentral gyrus
		686	−6, −8, 62		SMA + medial precentral gyrus
		560	−60, −30, 26		IPL
		151	−48, −68, 6		STG + middle temporal gyrus
		111	−46, 13, 31		DLPFC
		104	−42, 40, −6		Ventral middle frontal gyrus
		77	−2, 16, 38		Anterior cingulated
		71	−28, −18, 8		Posterior lentiform nucleus
		32	−12, −38, 66		Post-central + precentral gyri
		25	−6, −26, −16		Red nucleus
		20	−42, −2, 56		Premotor cortex
		18	−34, −12, 54		Anterior precentral gyrus
		630	16, 2, 60	**Right**	SMA
		259	54, 16, 0		STG
		81	26, −72, −38		Cerebellum, pyramis
		67	26, −18, 52		Precentral gyrus
		45	32, −64, −26		Cerebellum, declive
		23	30, −44, 56		IPL + intraparietal sulcus
SCI	Imagine versus rest	28	−4, −28, 58	**Left**	SMA + medial precentral gyrus
		20	−10, −44, −22		Cerebellum, culmen
		60	16, −36, −34	Right	pons + anterior cerebellum
		21	12, −6, 64		SMA
		18	48, −40, −18		Fusiform gyrus
		18	312, −42, −22		Cerebellum, culmen

Findings in largest, and key motor, activation clusters are reported, at threshold of $P < 0.001$. Cluster size is in 2 mm^3 voxels. Coordinates are in MNI stereotaxic space. The suggestion of an anterior translocation of left primary sensorimotor cortex activation in patients during attempted movement is actually due to fusion of several separate foci (Fig. 2); a significant subfocus at (−6, −26, 56) present in controls was at a site similar to patients (−4, −24, 62).

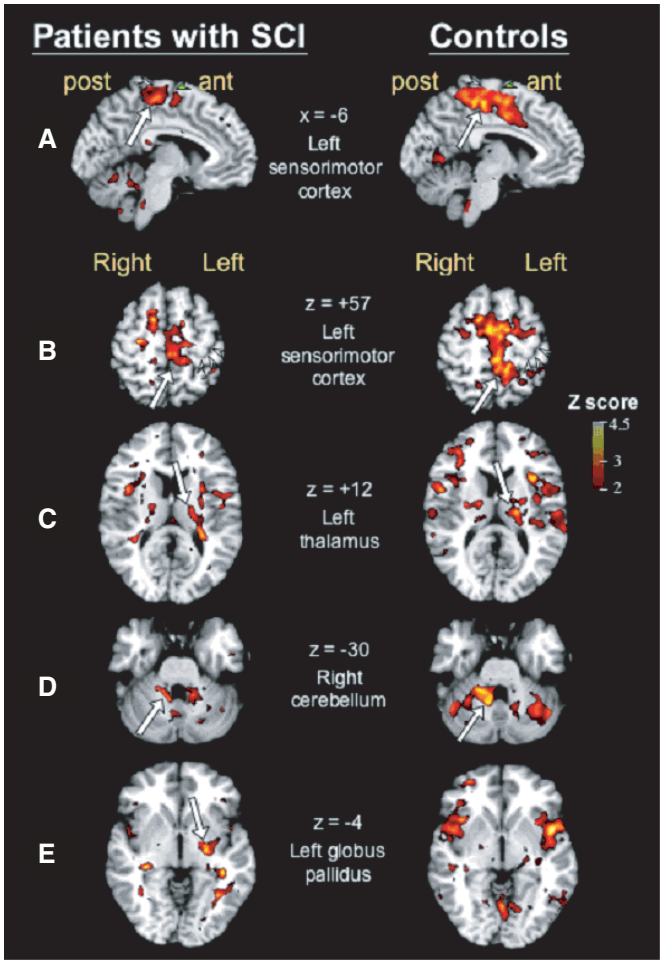

Fig. 2 Functional MRI of attempted right foot movement. Patients with SCI show activation that is in a similar site as controls but smaller in volume in (**A**)/(**B**) left sensorimotor cortex, (**C**) left thalamus including ventrolateral nucleus and (**D**) right cerebellum. Patients with SCI, but not controls, showed significant activation in the internal segment of left globus pallidus, shown in (**E**). Data are group activation maps and correspond to Table 2. The x and z values (centre column) indicate imaging plane in MNI stereotaxic space. White arrows indicate brain region of interest; white arrowheads, the central sulcus; green arrowheads, precentral sulcus.

internal segment of left globus pallidus, an area not significantly activated in controls (Fig. 2E). This was accompanied by activation in left ventrolateral thalamus (Fig. 2C), the volume of which was approximately the same as activation volume in controls (Table 2).

Among patients, increased age correlated with increased activation in the anterior lobe of the right cerebellum. ASIA sensory score, ASIA motor score, time since SCI and perceived difficulty of imagining movement did not correlate significantly with activation in any brain area.

Controls and patients with SCI both showed a similar signal increase during attempted movement in mesial precentral gyrus and post-central gyrus on the left, contralateral to movement (Fig. 3). The variance in signal change was higher

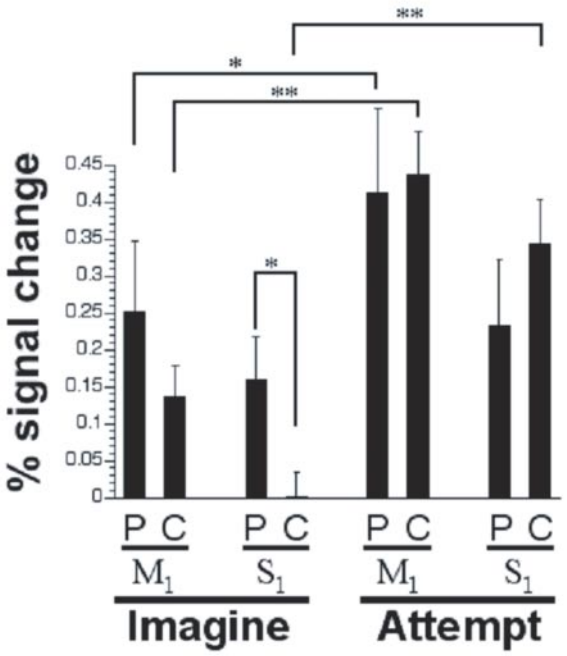

Fig. 3 Task-related signal change in mesial cortex of precentral gyrus (M_1) and of post-central gyrus (S_1). Values are mean ± SEM. P = patients with SCI, C = Controls, **P* < 0.05, ***P* < 0.0005 using paired testing.

for patients in both precentral (1.94 times the value of controls) and post-central gyri (1.49 times the value of controls).

Imagined movement

In controls (Table 2), activation was present in a cortical–subcortical motor network (left mesial primary sensorimotor cortex, bilateral SMA, left basal ganglia, left red nucleus and right cerebellum), motor imitation areas (bilateral superior temporal gyrus + sulcus, left ventral premotor cortex) (Iacoboni *et al.*, 1999; Nishitani *et al.*, 2004) and attention-related areas [bilateral inferior parietal lobule (IPL), left dorsolateral prefrontal cortex (DLPFC), and left anterior cingulate]. Increased age correlated with increased activation in the right parahippocampal gyrus.

Patients with SCI activated many areas identified in controls during imagined right foot movement, and again the volume of significant activation peaks was smaller than in controls. The largest contralateral activation cluster in patients, left mesial precentral gyrus + SMA, was 4% of the volume in controls and was 20 mm posterior. Among patients, increased age correlated with increased activation in the left putamen, left red nucleus and bilateral caudate head. Time since SCI correlated with increased activation within left SMA. ASIA sensory score, ASIA motor score and perceived difficulty of imagining movement did not correlate significantly with activation in any brain area.

During imagined right foot movement, controls and patients with SCI both showed a signal increase in left

precentral gyrus. However, a signal increase in post-central gyrus was absent in controls and seen only in patients (Fig. 3). The variance in signal change was again higher for patients in both precentral (2.34 times the value of controls) and post-central gyri (1.67 times the value of controls).

When directly contrasting fMRI maps between patients with SCI and controls, few significant differences were found. The comparison 'patients with SCI—controls' showed a significant focus of activation in the left STG/sulcus for each task. The comparison 'controls—patients with SCI' did not show significant foci for either task.

Modulating task (attempt versus imagine)

In controls (Table 3), direct contrast of activation maps found that attempted movement activated more than imagined movement did in three main areas: left primary sensorimotor cortex, right dorsal cerebellum and right secondary somatosensory area. Imagined movement activated more than attempted movement did in several foci, including left DLPFC and right precentral gyrus. In patients with SCI, there were no significant foci of modulation when attempted and imagined movements were directly contrasted in a two-tailed manner. However, for the signal change analysis, which was a within-subject comparison, both controls and patients with SCI showed a boost in precentral gyrus signal for attempted movement as compared with imagined movement (Fig. 3).

Modulating force level (low versus high)

For each task and each subject group, there were differences in brain activation between low (L) and high (H) force blocks, more for L–H than for H–L (Table 3). For controls, changing force level modulated activity in sensory and motor areas

Table 3 Modulation of task and of force level

Group	Task	Cluster size	Coordinates	Brain region	
Modulate task					
Control	Attempt–Imagine	27	−8, −30, 66	**Left**	precentral gyrus
		20	−14, −40, 64		Post-central gyrus
		16	6, −50, −18	**Right**	cerebellum, culmen
		14	62, −28, 20		Parietal operculum (SII)
	Imagine–Attempt	46	−38, 8, 44	**Left**	DLPFC
		14	−14, 24, 50		Premotor cortex
		29	8, 50, 28	**Right**	medial prefrontal
		24	34, −22, 54		Precentral gyrus
Modulate force					
Control	Attempt L–H	33	−32, −12, 18	**Left**	insula
	Attempt H–L	16	32, −72, 24	**Right**	occipital lobe
	Imagine L–H	24	−2, −72, 22	**Left**	precuneus
		17	−38, −72, −3		Inferior occipital gyrus
		16	−48, −46, −18		Fusiform gyrus
		14	−46, −26, 22		Parietal operculum (SII)
	Imagine H–L	16	12, −40, −24	**Right**	cerebellum, culmen
SCI	Attempt L–H	35	−60, −46, 20	**Left**	STG
		30	−12, −8, 68		SMA
		29	0, 10, 46		Pre-SMA (bilaterally)
		25	−2, 10, 48		SMA + pre-SMA
		21	−28, 0, 50		Premotor cortex
		16	−2, −20, 62		Medial precentral gyrus + SMA
		15	−48, −22, 2		STG
		14	−42, 4, 32		Inferior frontal gyrus ventrally
		46	22, 18, 54	**Right**	medial superior frontal gyrus
		26	8, 34, 20		Anterior cingulated
		26	46, 16, −8		STG + inferior frontal gyrus
		25	32, 20, 42		DLPFC
		20	34, 52, 18		Superior frontal gyrus, ventrally
		18	12, 6, 44		Anterior cingulated
		18	12, −50, −26		Cerebellum, dentate
		17	56, −30, 10		STG
		12	14, −54, 58		Precuneus
	Imagine L–H	25	−46, −22, 14	**Left**	parietal operculum (SII)
		18	−32, −54, 14		Temporal lobe
		13	−34, −42, −12		Parahippocampal gyrus
		30	44, −18, 8	**Right**	insula

Findings in activation clusters are reported at threshold of $P < 0.001$. Cluster size is in 2 mm^3 voxels. Coordinates are in MNI stereotaxic space. L and H refer to low and high force movements, respectively.

including precuneus and dorsal cerebellum. Results in patients with SCI had limited overlap with findings in controls and included parahippocampal gyrus.

Discussion

The current study aimed to evaluate motor system function in patients with chronic, complete SCI. The main result was that patients with chronic SCI, while retaining many features of normal brain motor function, also showed: (i) reduced activation volume, supporting the study hypothesis, along with increased variance; (ii) brain activation patterns not seen in controls, particularly increased pallido–thalamocortical loop activity during attempted movement and abnormal processing in primary sensorimotor cortex during imagined movement; and (iii) abnormal modulation of brain activity with change in movement task or force. Therefore, although some features of motor system activation persist after chronic, complete SCI, the cerebral component of voluntary movement is not normal. Such brain functions are critical to voluntary movement, and therefore these SCI-associated abnormalities have the potential to reduce effectiveness of treatments aiming to restore movement in this population.

During attempted right foot movement, many features of the activation pattern found in controls were preserved in patients with SCI. Examples include activation of a movement-related circuit that included left precentral gyrus, left thalamus, bilateral SMA, right cerebellum and right anterior cingulate. These similarities in fMRI findings were found despite the significant difference in EMG, being active in controls but silent in patients (Fig. 1). Also, both subject groups showed similar precentral gyrus and post-central gyrus signal change during attempted movement (Fig. 3). Furthermore, in a within-subject comparison, both controls and patients with SCI modulated precentral gyrus signal with change in foot task (Fig. 3), as described previously in healthy subjects (Porro *et al.*, 1996; Grezes and Decety, 2001). These findings of preserved sensorimotor cortex function years after SCI are concordant with a prior report that paraesthesias can be evoked by cortical stimulation in the deafferented limbs of patients with chronic SCI (Cohen *et al.*, 1991).

During imagined right foot movement, many features of brain activation found in controls were again preserved in patients with chronic SCI. Both groups activated a motor circuit that included left precentral gyrus, left SMA and dorsal right cerebellum during this task. Imagined movement is of particular interest as a motor system probe because actual limb movement (EMG recordings, Fig. 1) and motor imagery skill (performance on motor imagery assessment, Table 1) were identical between the two subject groups. However, a comparison of control and patient brain map data acquired during motor imagery is complicated by the fact that motor state and motor experience influence motor imagery performance (Guillot and Collet, 2005), though studies disagree as to the influence of motor system injuries such as stroke and SCI (Decety and Boisson, 1990; Lacourse *et al.*, 1999; Johnson *et al.*, 2002). The motor experience of the current healthy control subjects, including their foot movements during pre-scan rehearsal, likely influenced the brain processes underlying motor imagery, relative to patients with SCI. Thus while motor imagery, as compared with motor execution, matches motor system output between subjects, the experience of motor imagery might not involve identical brain events across subject groups.

However, there were a number of differences between the two subject groups. Patients with SCI activated the left superior temporal gyrus/sulcus more than controls did for each task, possibly reflecting abnormal motor imitation (Iacoboni *et al.*, 1999; Nishitani *et al.*, 2004) or perhaps altered auditory attention. Also, changing tasks did not modulate brain activity in a normal way in patients with SCI. Among controls, activation was greater in areas related to motor output during attempted movement, while activation was greater in areas related to attention and complexity during imagined movement. Patients with SCI, however, did not show any of these modulations (Table 3). Also, patients failed to show the normal modulation of activity in post-central gyrus between tasks (Fig. 3). This difference between groups in post-central gyrus might reflect an SCI-associated abnormality of processing in primary sensorimotor cortex, though this finding might in part be explained by the fact that controls, but not patients, had a difference in sensory input between tasks.

Modulation of brain activity between force levels was also not normal in patients with SCI. In controls, change in brain activity between force levels was less than expected, but was consistent with the similarity of EMG measures found between high and low force (Fig. 1). In patients with SCI, change in force level was associated with altered activity within a number of brain regions, most of which did not modulate activity in controls. While most of these regions are associated with either motor function or attention, these, nevertheless, represent a separate pattern of motor system abnormality after SCI.

Activation volumes in patients were substantially smaller than in controls. This might in part reflect efferent motor system events, and might in part reflect reduced sensory input after complete SCI, especially during attempted movement. Few of these differences in activation volume reached significance when the two groups were directly contrasted, a finding that might be due to sample size or to the fact that inter-subject variance in motor cortex fMRI measures was approximately twice as high in patients (Fig. 3). These fMRI measures of variance are similar to previous electrophysiological studies in patients with chronic complete SCI, which described twice the normal inter-subject variance (Lacourse *et al.*, 1999). In a prior study, patients with hemiplegic stroke had reduced regional activation volumes with preserved signal change versus controls (Cramer *et al.*, 2002*a*). In the current study, the same pattern of reduced activation volume with preserved signal change was again seen, in precentral and post-central gyri. Prior electrophysiological observations

show that amplitude and latency of motor cortical potentials are reduced after SCI (Green *et al.*, 1999; Lacourse *et al.*, 1999). Collectively, these findings suggest that neuronal activity in brain areas related to motor control of a plegic limb is preserved but disorganized, operating with twice normal variability.

The current results suggest that chronic, complete SCI is associated with disordered basal ganglia influence upon thalamus, and thus cortex, in the form of increased pallido–thalamocortical loop (Middleton and Strick, 2000) recruitment. Patients with SCI had significant activation in the internal segment of the globus pallidus during attempted movement but controls did not (Fig. 2E). Though this area projects to several brain regions (Parent and Parent, 2004), pallidal projections to thalamus are most likely altered after SCI, as ventrolateral thalamic activation in patients (Fig. 2C) was relatively high at 92% of control activation volume. Increased pallido–thalamocortical activity could represent increased excitation or inhibition, not distinguished by current fMRI methods. This finding could represent a pathological attempt to regulate the rate of change of force (Vaillancourt *et al.*, 2004). Whether this activity is a help or a hindrance to restorative interventions remains to be determined, but the finding might represent an obstacle to restoring motor function in this population because it indicates neuronal events not normally found during this task.

A posterior shift in contralateral sensorimotor cortex activation site of 20 mm was present in patients with SCI during imagined movement. This is consistent with prior studies in a range of neurological conditions (Green *et al.*, 1998, 1999; Cramer *et al.*, 2000; Lee *et al.*, 2000; Pineiro *et al.*, 2001; Turner *et al.*, 2003).

Divergent results have been reported in prior functional neuroimaging studies of the brain motor system after SCI. This might in part be due to variability in a number of factors that relate to motor outcome after SCI (Maynard *et al.*, 1979; Crozier *et al.*, 1991; Donovan *et al.*, 1992; Silberstein *et al.*, 1992; Katoh *et al.*, 1996; Curt and Dietz, 1999; Calancie *et al.*, 2004). Sabbah *et al.* (2002) described smaller activation versus controls during attempted toe flexion in nine patients, mean age 36 years, 10 years after SCI at T6–L2 level, with or without preserved sensation. Though these results are in general agreement with current findings, direct comparison is limited owing to absence in this paper of inter-group statistical comparisons, specific activation locations, data on subcortical areas and activation volumes. Alkadhi *et al.*, (2005) reported brain motor area activations to be significantly greater than controls during imagined 0.5 Hz right ankle movements in eight patients, mean age 31 years, 2.7 years after complete SCI at T3–L1 level. These two studies and the current report differ in many aspects, each of which could have an important effect on results, including sample size, subject age, duration of SCI, degree to which SCI is complete and the task used to activate the brain. Humphrey *et al.*, (2000) addressed one of these issues in patients with paraplegia: increasing duration of SCI was associated with reduced activation in regions of motor cortex, during attempted foot movement. The specific motor regions were not stated, making difficult a direct comparison with the current study, which found that increasing duration of SCI was associated with increased activation within SMA, during imagined movement. Also, the current study found several examples whereby the related variable age correlated with increased motor system activation after SCI, during either task. As is the case for stroke (Cramer, 2004), variables such as demographics and injury are important determinants of motor reorganization after SCI.

The results in patients with SCI support a direct role for primary sensory cortex in the genesis of behaviour. Several lines of evidence suggest that post-central gyrus might have a direct role in the generation of movement (Bornschlegl and Asanuma, 1987; Pavlides *et al.*, 1993) including data derived from anatomical (Galea and Darian-Smith, 1994), cortical stimulation (Graham-Brown, 1914; Woolsey, 1958) and neurophysiological recordings (Soso and Fetz, 1980; Fromm and Evarts, 1982; Wannier *et al.*, 1991; Ikeda and Shibasaki, 1992). However, in healthy humans, functional neuroimaging of post-central gyrus during voluntary movement does not distinguish efferent signals from sensory feedback. The current study examined post-central gyrus activity in patients with complete SCI, among whom clinical exam suggested absence of sensory feedback. Results support that post-central gyrus activity during movement is not limited to afferent signal processing in humans, but do not distinguish whether this post-central gyrus activity represents motor output or sensorimotor processing. However, somatosensory evoked potentials persist in a minority of patients with complete infralesional sensory loss (Dimitrijevic *et al.*, 1983). Because no somatosensory evoked potential data were collected on current study patients, a contribution to post-central gyrus activation by afferent signal processing cannot be fully excluded, and further studies are needed to draw more definitive conclusions.

The significance of the abnormalities of brain function observed in patients with SCI is not clear, but several considerations suggest a loss of function. Patients with SCI showed smaller motor cortex activation volumes (Fig. 2 and Table 2). Smaller activation is normally associated with weaker force output (Dettmers *et al.*, 1995; Cramer *et al.*, 2002*b*; Ward and Frackowiak, 2003) and with slower rate of movement (Rao *et al.*, 1996; Schlaug *et al.*, 1996). Patients with SCI also failed to show the normal pattern of motor cortex activity modulation across the two foot tasks. Failure to modulate a cortical region's activity across tasks has in some paradigms correlated with inability to modulate corresponding behaviours (Jones *et al.*, 2000; Thomsen *et al.*, 2004; Dirnberger *et al.*, 2005). Together, these considerations suggest a loss of motor cortex function after chronic, complete SCI. The basis for this probably includes reduced motor system output to the lower extremity, analogous to the fact that the motor cortex representation is expanded for practised movements but stable or contracted for non-practised

movements (Karni *et al.*, 1996; Nudo *et al.*, 1996; Floyer-Lea and Matthews, 2005; Martin *et al.*, 2005), or that motor evoked potentials are reduced after chronic limb immobilization (Kaneko *et al.*, 2003; Zanette *et al.*, 2004; Martin *et al.*, 2005). Reduced sensory input also probably contributed to these fMRI findings in patients with SCI (Asanuma *et al.*, 1986; Coq and Xerri, 1999; Zanette *et al.*, 2004). Findings might also in part reflect direct effects of SCI pathology upon the brain. Whatever their basis, the fMRI abnormalities seen in patients with SCI probably correspond to a loss of brain motor system function, a factor of potential importance to therapies aiming to restore movement after SCI.

Overall, the current results provide evidence that many features of brain motor system function are intact after chronic complete SCI, though with dampened magnitude and increased variance. The findings support the potential for therapies that aim to restore movement after SCI because fundamental aspects of motor system reorganization remain apparent. However, patients with SCI exhibited several abnormal features of brain activation not seen in normal subjects, and also failed to modulate brain activity with change in task load or type. Such patterns suggest a loss of motor cortex function, and raise concern that brain events that normally occur during voluntary movement are substantially deranged after complete SCI. The extent to which this is true in a less chronic population, or a population with incomplete SCI, requires further study. For therapies that aim to restore motor function after SCI, deranged brain function means that movement initiation might not occur normally. Therefore, addressing these changes in the cerebral component of volitional movement may be important to most effectively implementing restorative therapies for patients with SCI.

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