### Title
Effects of motor imagery training after chronic, complete spinal cord injury.




### Journal
Experimental brain research, 177(2)

### ISSN
0014-4819



### Authors
Cramer, Steven C
Orr, Elizabeth LR
Cohen, Michael J
et al.



### Publication Date
2007-02-01

### DOI
10.1007/s00221-006-0662-9

Exp Brain Res (2007) 177:233–242
DOI 10.1007/s00221-006-0662-9

RESEARCH ARTICLE

# Effects of motor imagery training after chronic, complete spinal cord injury

**Steven C. Cramer · Elizabeth L. R. Orr · Michael J. Cohen · Michael G. Lacourse**

Received: 22 May 2006 / Accepted: 1 August 2006 / Published online: 31 August 2006


**Abstract** Abnormalities in brain motor system function are present following spinal cord injury (SCI) and could reduce effectiveness of restorative interventions. Motor imagery training, which can improve motor behavior and modulate brain function, might address this concern but has not been examined in subjects with SCI. Ten subjects with SCI and complete tetra-/paraplegia plus ten healthy controls underwent assessment before and after 7 days of motor imagery training to tongue and to foot. Motor imagery training significantly improved the behavioral outcome measure, speed of movement, in non-paralyzed muscles. Training was also associated with increased fMRI activation in left putamen, an area associated with motor learning, during attempted right foot movement in both groups, despite foot movements being present in controls and absent in subjects with SCI. This fMRI change was absent in a second healthy control group serially imaged without training. In subjects with SCI, training exaggerated, rather than normalized, baseline derangement of left globus pallidus activation. The current study found that motor imagery training improves motor performance and alters brain function in subjects with complete SCI despite lack of voluntary motor control and peripheral feedback. These effects of motor imagery training on brain function have not been previously described in a neurologically impaired population, and were similar to those found in healthy controls. Motor imagery might be of value as one component of a restorative intervention.

**Keywords** Motor system · Imagery · Plasticity · Putamen · Globus pallidus · Spinal cord injury

S. C. Cramer · E. L. R. Orr
Departments of Neurology and Anatomy and Neurobiology, Associate, Reeve-Irvine Research Center, University of California, Irvine, USA

E. L. R. Orr · M. J. Cohen · M. G. Lacourse
V.A. Long Beach Neuroimaging Research Lab, Long Beach, USA

M. J. Cohen
Department of Psychiatry and Human Behavior, University of California, Irvine, USA

M. G. Lacourse
Deparment of Kinesiology, California State University, Long Beach, USA

S. C. Cramer (✉)
UCI Medical Center, University of California, Irvine, 101 The City Drive South, Building 53 Room 203, Orange, CA 92868-4280, USA
e-mail: scramer@uci.edu

Spinal cord injury (SCI) is a common neurological condition associated with substantial motor disability. Several therapeutic approaches are under investigation towards reducing disability after SCI. Some focus on SCI repair (Raineteau et al. 2002; Dobkin and Havton 2004), while others aim to drive muscles or devices with signals derived from cortical recordings (Carmena et al. 2003; Friehs et al. 2004; Scherberger et al. 2005).

Such approaches generally assume intact brain motor systems for driving limb movements. However, although brain mapping studies have found preservation of many normal features of motor system function after SCI, abnormalities of brain motor system function have also been described. Examples include both sub- and supra-normal activation in motor system foci (Sabbah et al. 2002; Alkadhi et al. 2005; Cramer et al.

2005), higher threshold and longer latency for motor evoked potentials to muscles below an incomplete lesion (Davey et al. 1998; Curt and Dietz 1999), and enhanced excitability of motor pathways targeting muscles above the level of SCI (Topka et al. 1991). These abnormalities likely represent effects of impaired corticospinal tract integrity and peripheral feedback, as well as reactive/adaptive changes in brain function.

Normalization of brain motor system function might be useful as an adjunct to therapies aiming to restore movement after SCI, and motor imagery training might be one means to achieve this. This form of training involves internal reactivation of the representation of a specific motor action without any overt motor output, and is governed by the principles of central motor control (Sharma et al. 2006). Motor imagery can modify brain function and improve motor performance in healthy controls; in subjects with neurological impairment, motor imagery can improve motor performance but little is known regarding effects on brain function (Pascual-Leone et al. 1995; Gerardin et al. 2000; Page et al. 2001; Jackson et al. 2003, 2004; Crosbie et al. 2004; Dijkerman et al. 2004; Johnson-Frey 2004; Lacourse et al. 2004a, 2005; Page et al. 2005). Ability to perform motor imagery is preserved after SCI (Decety and Boisson 1990; Lacourse et al. 1999), though the capability of motor imagery to modify motor behavior or brain motor system function in subjects with SCI has not been studied to date.

The current study examined the effects of a 7-day course of motor imagery training on a body area that did (tongue) and an area that did not (right foot) retain voluntary motor control after SCI. The content of training was imagined movement of tongue, and separately of right foot, through a 5-part sequence using audiovisual cueing provided by an in-home computer. Assessments were made before and after training. The primary behavioral outcome measure was the rate with which this same 5-part sequence was actually performed. Functional MRI was used to probe brain function. Though the intervention revolved around imagined movement, the fMRI task employed attempted movement given that the long-term goal is to improve brain function related to moving the plegic limb. Neurophysiological assessments were made using transcranial magnetic stimulation (TMS).

We hypothesized that behavioral effects of motor imagery would be similar among subjects with complete SCI and healthy controls for tongue movements, as imagery was expected to remain intact for supralesional muscles. For foot movements, imagery effects on behavior were hypothesized to be different among these two subject groups, with gains in controls but no change in subjects with SCI—imagery was not expected to modify chronic complete plegia, but when used as an adjunct, the effects of imagery on brain function might improve the impact of other restorative interventions.

The main focus of this study revolved around the hypothesis that motor imagery training would induce similar changes in brain motor system activation during attempted movement among controls and subjects with SCI, despite absence of voluntary movement in the latter. This was based on prior studies in healthy subjects showing that motor system activation can be modified by a 1-week course of motor imagery practice, i.e., by an intervention that lacked physical movement rehearsal (Pascual-Leone et al. 1995; Jackson et al. 2003; Lacourse et al. 2004a).

As a corollary, we further hypothesized that motor imagery training would reduce abnormalities of brain motor system function seen at baseline in subjects with SCI, a question of particular interest given the paucity of data examining effects of imagery training on brain function in a neurologically impaired population. This hypothesis arose from the fact that motor imagery is known to improve motor behavior, and that in healthy subjects much of this improvement arises from changes in brain function. Brain motor system function is known to be deficient after SCI, therefore the ability of motor imagery to induce improvements was examined. The main focus was on contralateral putamen, thalamus, primary sensory, and primary motor cortex, given the key nature of these areas in movement generation and learning (Jueptner and Weiller 1998; Milliken et al. 1999; Maillard et al. 2000; Scholz et al. 2000; Doyon et al. 2003; Dobkin et al. 2004; Cramer et al. 2005). Motor imagery training was also hypothesized to reduce TMS thresholds for foot motor system activation over time based on a previous study of hand motor imagery effects in healthy subjects (Pascual-Leone et al. 1995).

## Materials and methods

### Subjects

Subjects with SCI had injury between C5 and T10, SCI >1 year prior to study enrollment, complete infralesional motor loss i.e., American Spinal Injury Association (ASIA) Impairment Scale Grade A or B, age <80 years, and no additional neurological diagnoses. Control subjects were age-matched to subjects with SCI and neurologically healthy. Subjects could have no major psychiatric diagnoses, nor contraindications to

MRI or TMS; the latter include certain metals in the body, pregnancy, and medications that lower seizure threshold such as tricyclic antidepressants or neuroleptics. The study was approved by the Institutional Review Board at the University of California, Irvine.

Study participation was 9 days long. On day 1, subjects underwent behavioral, fMRI, and TMS evaluations; days 2–8, 7 days of home motor imagery training for right foot and for tongue; and day 9, repeat of all baseline evaluations. Subjects with SCI and one set of healthy controls underwent complete testing and training. A second control group underwent serial fMRI scans only.

## Behavioral assessments

A medical history was obtained from each subject, as well as determination of handedness (Oldfield 1971) and footedness (Coren 1993). ASIA scores and Impairment Grade were measured. Maximum right foot (a) dorsiflexion force and (b) tapping rate across 10° were measured.

The primary behavioral outcome measure to assess effects of motor imagery training was the maximum rate of physical tapping of a 5-part sequence, determined separately for tongue and for right foot. Note that the 5-part sequence used to test behavior was also the one that was mentally rehearsed as content of imagery training. Tapping rate was measured using separate foot and tongue sensor plates. Each plate had four numbered, spatially separate contact stations that together subtended 45°. For the tongue, the head was restrained and the plate was suspended in front of the mouth so that the tongue could reach each of the four stations without head or jaw movement. For the right foot, a sock was donned that limited sensor plate contact to the plantar hallux. A sensor plate on the floor allowed the toe to reach each station by rotating the foot in the plane of the floor with the heel held stationary. Each sensor plate station detected tongue, or right hallux, contact, which was amplified (2000×, Grass-Telefactor), digitally converted (Maclab, ADInstruments), and recorded. Subjects repeated 5-part sequence tapping onto the sensor plate at maximum rate over 30 s. Two 5-part sequences were evaluated, in random order, on tongue then on right foot: “14213”, the sequence also used as motor imagery training content; and “41342”, a control sequence that was evaluated but not practiced.

## Functional MRI scanning

Subjects next prepared for fMRI by watching two videos, outside the scanner. Video 1 helped subjects understand the task to be performed. A right foot was shown hovering above an object, then moving in plantarflexion to crush the object.

Video 2 alternated 30-s blocks of rest and active state. For rest, subjects viewed images of a foot at rest, (new image every 3 s) and were instructed to remain at rest. For active state, subjects viewed images of a foot hovering above an object (new object every 3 s) and were instructed to attempt plantarflexion to crush each new object, regardless of whether their right foot was able to move or not. Bilateral ankle splints (Dobkin et al. 2004) that went from lower tibia to toes were also placed, restricting movement to 10° of ankle dorsiflexion/plantarflexion and preventing lateral leg rotation. During this rehearsal, surface EMG leads were attached to bilateral tibialis anterior muscles, with signal filtered (band pass 30/1,000 Hz), amplified, digitalized, and recorded.

During MRI scanning, subjects wore protective headphones, video goggles, the ankle splints, and had arms at side plus head stabilized. Scanning (1.5 T, Philips) began with a whole brain high-resolution volumetric anatomical scan (in-plane resolution 0.94 $mm^2$, slice thickness 1 mm). Functional scans were acquired next, with a gradient-echo echoplanar imaging sequence, axial slices = 4 mm thick with 1 mm gap, TE = 40 ms, TR = 3 s, flip angle = 80°, FOV = 24 cm, and acquisition matrix 128 × 128. A total of 170 volumes were acquired while video 2 guided subjects through alternating rest with attempted right foot movement. During fMRI, a member of the study team observed the subject, noting movement in any of the four extremities.

## Transcranial magnetic stimulation

Each subject’s volumetric MRI scan was registered to the subject’s head using Brainsight (Rogue Research, Inc.). Surface EMG leads were placed over the right tibialis anterior. A 70-mm figure of eight coil was placed over left medial central sulcus, with coil handle parallel to the sagittal sulcus. Using frameless stereotaxic TMS, the coil was systematically moved across a 5 × 8 $cm^2$ region that included mesial aspects of both hemispheres to identify the site with the lowest threshold for motor evoked response (>50 μV in at least 4 of 7 trials). Stimulation was adjusted in 1% TMS machine output increments.

## Motor imagery training

The day after baseline assessments, a member of the research team set up a computer in each subject’s

home. Instructions for the motor imagery were read aloud, then the subject demonstrated correct participation of training, i.e., imagery without actual movement. The subject then practiced motor imagery training for two 60-min sessions per day (30 min for right foot and 30 min for tongue in the a.m.; same in p.m.) for 7 days, recorded by the computer's camera. During training, audiovisual computer output guided the subject to imagine movement through the "14213" sequence, with a replica of the sensor plates having been placed adjacent to the body part undergoing motor imagery. A research team member phoned the subject every 3 days to offer assistance. Compliance was judged to be full or not for each session based on three factors: (1) subject interviews during phone calls, (2) length of each practice session, with only sessions of full duration considered compliant; and (3) subject attention, assessed by whether subjects responded correctly to computer-generated questions regarding the number of sequence repetitions performed during a pre-announced test period each day.

Exam, MRI, and TMS were repeated the day after completion of motor imagery training.

### Data analysis

Parametric statistics were used. For EMG data, the root mean square values were determined for the first 20 s of the first two rest and active blocks. 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 behavioral data, effects of time were examined using repeated measures ANOVA. Groups were directly compared using the Student *t*-test.

From each fMRI scan, several measures of left hemisphere motor system activation were extracted, including *volume*, *location*, and *magnitude* of activation. To derive these three measures, an activation map for individual subjects was created, for each of the two visits, using SPM2. The first two functional volumes were removed because of tissue non-saturation. Next, remaining images were realigned, coregistered to the volumetric scan, spatially normalized, transformed into MNI stereotaxic space, and spatially smoothed (4 mm FWHM). Images during attempted right foot movement were contrasted with rest for the activation map of each individual subject. Images showing excess head motion, defined as zero areas of brain activation, activation along more than 90° at the edge of the brain, or massive activation across all brain areas, were excluded.

Activation *volume* was measured ($P < 0.001$, using small volume correction) within left posterior putamen, thalamus, globus pallidus, and foot primary sensorimotor cortex (Fig. 1). The posterior aspect of putamen was examined because repetitive movements preferentially activate this portion (Jueptner and Weiller 1998). Posterior putamen, thalamus, and globus pallidus were drawn by hand on the SPM single-subject anatomical template, on which deep gray matter is well contrasted. Primary sensorimotor cortex for foot extended from precentral to postcentral sulcus, vertex to cingulate sulcus. Activation *location* was measured within each of these four areas as MNI $x$, $y$, and $z$ coordinates for center of activation, i.e., the center of mass. Activation *magnitude* was measured using MarsBaR (Brett et al. 2002) to extract task-related fMRI signal change in each subject's map within left posterior putamen, foot primary motor cortex, and foot primary sensory cortex. For activation magnitude, foot primary motor and sensory cortex were separated by the central sulcus, and included only the subset of voxels known to activate during foot movement in a prior control group (Cramer et al. 2005); note that none of the control subjects or subjects with SCI in the current study were part of that prior study. For each measure, a within group comparison evaluated the effect of time, for each of the three subject groups individually, as well as for the combined group representing all subjects treated with motor imagery training. Next, the two treated subject groups, and the two healthy control groups, were directly compared. No correction was made for multiple comparisons.

## Results

### Subjects

Of the ten subjects with SCI enrolled, eight were ASIA A (no infralesional sensorimotor function) and two were ASIA B (infralesional sensory but not motor function; Table 1). SCI level was C5 in five, C6 in one, T4 in one, T6 in two, and T10 in one. Subjects were studied $66 \pm 18$ months after SCI (mean $\pm$ SEM). There were no significant differences between the two treated groups in age or footedness (Table 1).

Three treated control subjects declined to complete the protocol resulting in recruitment of three new enrollees, and five fMRI studies were contaminated by excess head motion. This left 12 baseline and 9 post-training scans for treated healthy controls; 9 and 8 scans, respectively, for subjects with SCI; and 10

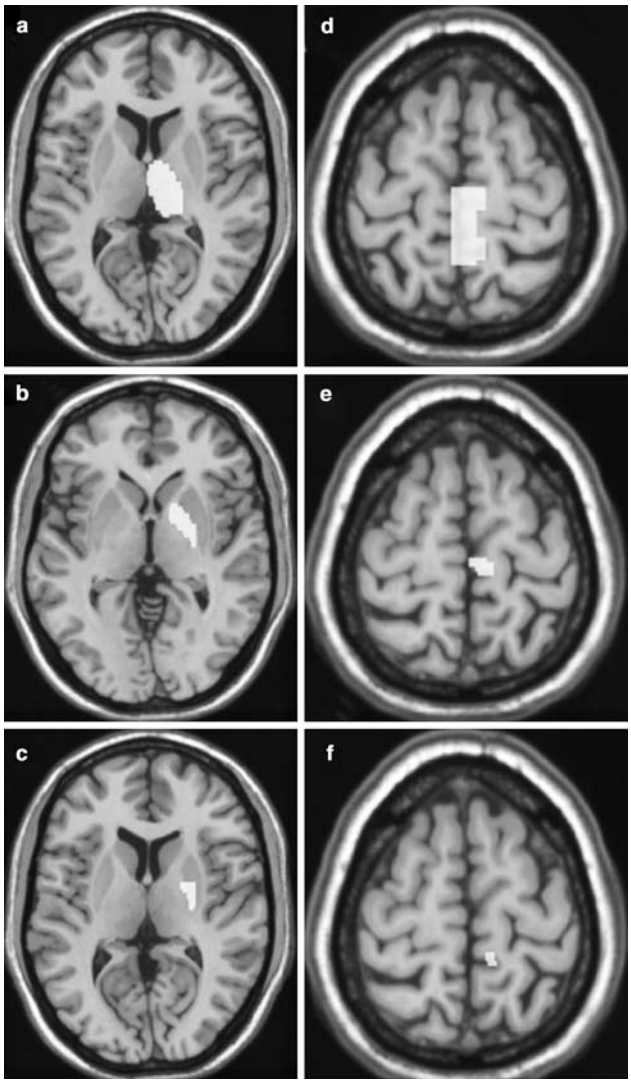


**Fig. 1** Representative slices from the regions of interest used in data analysis, all on left side of brain: **a** thalamus, **b** globus pallidus, **c** posterior putamen, **d** foot primary sensorimotor cortex, **e** the subset of foot primary motor cortex known to activate (at threshold $Z > 3$) during right foot movement from a prior study (Cramer et al. 2005), **f** the subset of foot primary sensory cortex known to activate (at threshold $Z > 3$) during right foot movement from a prior study (Cramer et al. 2005)

**Table 1** Clinical data

| | Subjects with SCI | Treated controls | Non-treated controls |
|---|---|---|---|
| *n* | 10 | 10 | 10 |
| Age (years) | 30 ± 4 | 32 ± 4 | 31 ± 3 |
| Footedness | 7R/2A/1L | 9R/1A | 10R |
| ASIA light touch | 53 ± 6* | 112 ± 0 | 112 ± 0 |
| ASIA pin | 33 ± 7* | 112 ± 0 | 112 ± 0 |
| ASIA motor | 31 ± 5* | 100 ± 0 | 100 ± 0 |

The two treated groups did not differ by age or footedness; nor by race or gender. Mean ± SEM. *R* Right, *A* ambipedal, *L* left

*$P < 0.0001$ comparing the two treated groups

and 10 scans, respectively, for the untreated healthy controls.

## Behavioral assessments

The two groups showed no significant difference in compliance with training. Full compliance during foot imagery training was present in 91 ± 4% of sessions by subjects with SCI versus 97 ± 2% of sessions by treated controls (mean ± SEM, $P > 0.2$). Full compliance was present for tongue imagery training in 90 ± 4% of sessions by subjects with SCI versus 98 ± 1% of treated controls ($P > 0.1$). Though not formally measured, a number of subjects with SCI reported fatigue in the plegic right foot immediately after training.

Over time, both treated groups showed improvement on the two tongue motor tasks (for patients, $P < 0.0005$ for the practiced task and $P < 0.05$ for the unpracticed task; for controls, $P < 0.0001$ and $P < 0.001$, respectively; Table 2). For the practiced tongue task, controls showed significantly larger gains over time than subjects with SCI ($P < 0.05$ for time × group interaction). For the unpracticed tongue task, there was no difference between groups in gains over time. Directly comparing the two treated groups found no significant differences on either task at either time point.

Study of the foot motor tasks in controls found a significant gain over time in the practiced ($P < 0.01$), but not the unpracticed, task. Subjects with SCI had no foot movement at either time point and thus no gains.

Training produced greater gains for the practiced task than for the unpracticed task. This was true both for the foot task ($P < 0.009$, controls only) and for the tongue task (examining both groups, $P < 0.05$, 2-tailed *t*-tests, with repeated measures time × group interaction not significant).

Treatment-related gains on the foot motor task in controls did not generalize to other foot motor measures. Neither maximum force (154 ± 22 N at baseline) nor tapping rate (3.7 ± 0.3 taps/s) changed over time in controls, with nil values at both time points in subjects with SCI.

## EMG

For both healthy control groups, at both time points, right tibialis anterior EMG during fMRI task rehearsal was significantly ($P < 0.05$) increased during movement as compared to rest, but left tibialis anterior EMG did not increase with movement. In subjects with SCI, EMG did not increase with attempted movement in either muscle at either time point.

**Table 2** Performance on tongue and foot motor tasks

| | Baseline | | Post-treatment | | % change over time | |
|---|---|---|---|---|---|---|
| | Treated controls | Subjects with SCI | Treated controls | Subjects with SCI | Treated controls | Subjects with SCI |
| *n* | 10 | 10 | 10 | 10 | 10 | 10 |
| Tongue, practiced | 1.4 ± 0.1 | 1.4 ± 0.2 | 2.3 ± 0.1 | 1.8 ± 0.2** | 74.6 ± 16 | 46.3 ± 10 |
| Tongue, unpracticed | 1.4 ± 0.2 | 1.2 ± 0.1 | 1.8 ± 0.1 | 1.6 ± 0.2 | 46.8 ± 15 | 30.9 ± 11 |
| Foot, practiced | 1.4 ± 0.1 | 0* | 1.9 ± 1.6 | 0* | 36.5 ± 9 | 0*** |
| Foot, unpracticed | 1.4 ± 0.1 | 0* | 1.5 ± 0.1 | 0* | 8.5 ± 6 | 0* |

Tongue and foot measures are reported in Hz. Mean ± SEM. Post-treatment data for tongue were lost due to computer error in one subject with SCI. For control versus subjects with SCI at a single timepoint, *$P < 0.0001$, **$P = 0.053$, ***$P = 0.001$

## Functional MRI

### *Task performance during scanning*

During fMRI, all controls performed isolated foot movements as instructed. In subjects with SCI, neither the right foot nor other extremities showed visible movement during fMRI with the exception of occasional minor right hand twitches in one subject with SCI pre-training and in two subjects post-training.

### *Activation site*

Over time, neither the MNI *x*, *y*, nor *z* location coordinate changed within left primary sensorimotor cortex, globus pallidus, thalamus, or posterior putamen. This was true in all three subject groups individually, as well as for the combined group representing all subjects treated with motor imagery training. Directly comparing the two treated groups at each time point disclosed one finding, that the *x*-coordinate for primary sensorimotor cortex activation at the second fMRI scan was more medial in subjects with SCI as versus treated controls (−1 vs. −5, $P < 0.03$); note that prior to therapy, the same coordinates were present but these did not reach significance. Directly comparing the two healthy control groups showed no significant differences.

### *Task-related signal change*

Over time, in the left posterior putamen, among all subjects treated with motor imagery training, task-related signal increased an average of 138 ± 67% ($P < 0.056$), without a significant time × group interaction. The non-treated control group did not show this significant change in left posterior putamen signal over time. Also, training was associated with no significant effect on task-related signal change within left M1 or S1 (Table 3). Over time, there were no other changes in any group or brain region. Directly comparing the two treated subject groups, as well as the two healthy control groups, at each time point disclosed no significant differences in any brain region.

### *Activation volume*

Over time, regional activation volume did not change significantly within left primary sensorimotor cortex, globus pallidus, thalamus, or posterior putamen (Table 3). This was true in all three subject groups individually, as well as for the combined group representing all subjects treated with motor imagery training. Subjects with SCI showed larger activation than the treated controls after training in left globus pallidus ($P < 0.054$) and posterior putamen ($P < 0.05$, see Fig. 2); note that in both regions, a trend in the same direction was present before training. There were no other significant differences in any brain region at either time point when the two treated subject groups, and when the two healthy control groups, were directly compared.

## Transcranial magnetic stimulation

In patients, no TMS response in right tibialis anterior could be elicited, either before or after motor imagery training. In controls, TMS response could be elicited from seven of the ten subjects, while in three subjects no response could be elicited at either TMS session, even at 100% of device output, at any scalp position. Among these seven, at baseline, mean TMS threshold was 78 ± 6% of device output, latency was 30.8 ± 1.6 ms, and motor evoked potentials averaged 97 ± 31 μVs. None of these TMS measures changed significantly over time.

# Discussion

Potential therapeutic interventions to reduce disability after SCI often assume intact brain motor system function

**Table 3** Functional MRI findings

| | Baseline | | | Post-treatment | | |
|---|---|---|---|---|---|---|
| | Controls (treated) | Subjects with SCI (treated) | Non-treated controls | Controls (treated) | Subjects with SCI (treated) | Non-treated controls |
| *n* | 12 | 9 | 10 | 9 | 8 | 10 |
| Task-related signal change | | | | | | |
| M1 | 0.27 ± 0.12 | 0.59 ± 0.17 | 0.39 ± 0.10 | 0.32 ± 0.08 | 0.68 ± 0.21 | 0.34 ± 0.08 |
| S1 | 0.11 ± 0.07 | 0.27 ± 0.10 | 0.14 ± 0.08 | 0.17 ± 0.05 | 0.26 ± 0.14 | 0.13 ± 0.06 |
| Posterior putamen | 0.05 ± 0.03 | 0.14 ± 0.13 | 0.02 ± 0.05 | 0.12 ± 0.05* | 0.21 ± 0.09* | 0.03 ± 0.02 |
| Regional activation volume | | | | | | |
| SMC | 419 ± 110 | 474 ± 127 | 524 ± 101 | 386 ± 86 | 435 ± 108 | 410 ± 100 |
| Posterior putamen | 11 ± 7 | 92 ± 44 | 32 ± 29 | 40 ± 26 | 141 ± 40^ | 13 ± 7 |
| Globus pallidus | 3 ± 2 | 50 ± 29 | 24 ± 21 | 12 ± 6 | 77 ± 32^ | 10 ± 5 |
| Thalamus | 79 ± 49 | 153 ± 100 | 70 ± 64 | 50 ± 35 | 126 ± 71 | 11 ± 7 |

All regions in left hemisphere. Mean ± SEM

*SMC* primary sensorimotor cortex, *M1* primary motor cortex, *S1* primary sensory cortex

*Task-related signal increased ($P < 0.056$) over time in left putamen in the two treated groups, but not in the untreated group

^After training, subjects with SCI showed larger activation volumes within left globus pallidus ($P < 0.054$) and putamen ($P < 0.05$) as compared to treated controls

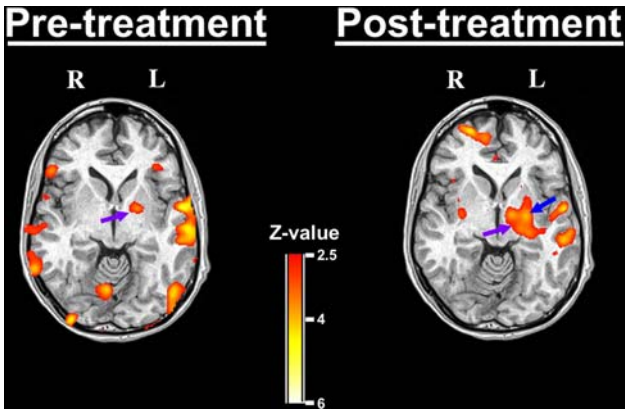


**Fig. 2** The fMRI activation maps are shown from a 32 year-old subject 2 years after a motor vehicle accident that resulted in complete (ASIA A) C6 tetraplegia An axial section at $z = +16$ is presented before and after 7 days of motor imagery treatment. At baseline, pre-training, left globus pallidus activation is evident (*purple arrow*). Post-training, an increase in activity is apparent in both left globus pallidus (*purple arrow*) and posterior putamen (*blue arrow*). The latter finding was significant across all treated subjects

(Raineteau et al. 2002; Carmena et al. 2003; Dobkin and Havton 2004; Friehs et al. 2004; Scherberger et al. 2005). However, abnormalities of brain motor system function have been described after chronic SCI (Topka et al. 1991; Sabbah et al. 2002; Alkadhi et al. 2005; Cramer et al. 2005), and these might require attention to achieve maximum therapeutic efficacy from new interventions. The current study hypothesized that motor imagery training would have similar effects in controls and subjects with plegic SCI on activation of the brain motor system related to attempted movement. In support of this, controls, who could move the right foot during fMRI, and subjects with SCI, who could not, showed increased left putamen activation after a week of foot motor imagery training. These effects of imagery training upon brain function have not been previously described in a neurologically impaired population. Together, these results suggest that brain motor system function can be modulated independently of voluntary motor control and peripheral feedback, and that motor imagery training might have value as an adjunct to restorative interventions targeting SCI.

Motor imagery training was used in the current study rather than physical practice. As compared to attempted physical movement, motor imagery is associated with reduced magnitude of brain activation (Porro et al. 1996), and as compared to physical exercise, motor imagery training produces smaller behavioral gains (Lacourse et al. 2004b). However, imagery offers certain advantages. From a study design point of view, this permitted closer matching of the intervention between subject groups. Also, motor imagery training might have clinical value in subjects with a weak limb, complementing the gains offered by physical exercise (Jeannerod and Frak 1999; Pomeroy et al. 2005; Sharma et al. 2006). For example, motor imagery allows a subject to mentally experience completion of a task in a paretic/plegic limb, subjects can sculpt a single movement step in a limb impaired by synkinetic movements, and imagery-based training can be administered independent of motor impairment level. Reports of fatigue after training by some subjects with SCI suggest that improvement in mental fitness is also a possibility.

The data support the hypotheses related to training effects on behavior, showing similar gains in tongue movement in both treated groups (Table 2), and showing gains in foot movement only in the healthy controls. Comparison of therapeutic behavioral gains in the current control group with published reports is limited by several factors. In treated controls of the current study, movement rate of the practiced task increased 36–75%. Three prior studies also employed the behavioral outcome measure as the content of 1-week motor imagery training in healthy controls. Lacourse et al (2004a) found an 86% increase in movement rate after training, but these authors' higher value might in part be due to study of a different body region, the right hand. Jackson et al (2003) studied the foot, but the endpoint was reaction time, which improved (decreased) by 10% after training. Pascual-Leone et al. (1995) found a 43% improvement (decrease) in right hand errors during performance of a fine motor skill.

The data also supported the hypothesis that training would be associated with similar changes in brain activation across controls and subjects with SCI. The training-related increase in left putamen activation was similar across the two treated groups, with no significant difference between the these two groups (Table 3), despite the fact that controls but not subjects with SCI could actually move the foot during scanning as instructed. The increase in putamen activation might reflect motor learning (Jueptner and Weiller 1998; Doyon et al. 2003), an interpretation supported by prior reports that motor imagery in healthy subjects improves motor performances (Pascual-Leone et al. 1995; Jackson et al. 2003; Lacourse et al. 2004a). The current data do not distinguish whether the motor system changes are related to planning, processing, or execution. However, the findings do suggest that at least some components of motor learning can take place in the complete absence of voluntary motor control.

Comparison of current results with prior serial brain mapping studies during motor imagery training in healthy subjects is complicated by differences in the brain mapping probe, treatment content, and study power. Increased orbitofrontal cortex (Jackson et al. 2003), as well as cerebellar, premotor, and striatal (Lacourse et al. 2004a), activation have been reported. Hypothesized changes in neurophysiology were not observed in the current study but were found in a prior serial brain mapping study by Pascual-Leone et al (1995). These authors gave healthy subjects similar imagery training as in the current study, but to the hand, and found reduced TMS thresholds over time. The basis for this difference is unclear but might relate to the higher baseline thresholds required to stimulate the foot area, which resides within the interhemispheric fissure, as compared to hand.

The study did not support the hypothesis that motor imagery training would reduce SCI-related baseline abnormalities in globus pallidus activation. A prior study using the same fMRI probe found that subjects with chronic, complete SCI had larger than normal activation volume in left globus pallidus (Cramer et al. 2005). In the current, smaller cohort, a baseline trend towards the same finding (Table 3) increased in significance after training. The meaning of this finding requires further study as well as replication using a different motor task, but globus pallidus activation has been associated with force regulation (Vaillancourt et al. 2004), speed of cognitive processing (Dirnberger et al. 2005), and with sensory gating of motor control (Kaji 2001). The current observations could represent derangement in one of these functions, or a dysfunction related to other movement disorders (Toda et al. 2004). Globus pallidus dysfunction after SCI requires further study and might reflect a process that is a barrier to restoring motor function.

Prior studies have also described abnormalities in leg primary sensorimotor cortex function using group map analyses, some finding subnormal (Humphrey et al. 2000; Sabbah et al. 2002; Cramer et al. 2005) and others finding supranormal (Alkadhi et al. 2005) activation. The current study was not powered to use these analyses, using a more sensitive region of interest approach instead, and did not identify differences between groups at baseline in primary sensorimotor cortex activation (Table 3). The current study did confirm the results of a prior study (Cramer et al. 2005) showing that left primary leg sensorimotor cortex activation during attempted right foot movement is more medial after chronic SCI as compared to activation during the same tasks in healthy subjects, a finding that might reflect a number of processes such as reduced sensory feedback or effects of motor disuse.

Whether future therapies to improve motor status after SCI focus on spinal cord repair or brain signal recordings, attending to abnormalities of brain function will likely be an important component to maximize gains. The current study found that the training-related increase in putamen activation present in controls was also present in subjects with SCI, but that training did not reduce SCI-associated baseline abnormalities of globus pallidus function. Strengths of the study include homogeneity of subject groups, high compliance with training, and inclusion of a serially scanned non-treated control group. Weaknesses include small

sample size, and lack of correction for multiple comparisons. The study would have been improved by addition of a fourth subject group, subjects with SCI who did not undergo motor imagery training and by addition of a fifth subject group, subjects with SCI who received sham training. The fMRI activation task was selected because of its demonstrated value (Cramer et al. 2005) for probing the brain motor system of interest, that related to attempted movement. However, this probe might have had reduced sensitivity to treatment-related changes in brain function because treatment and brain activation employed different tasks. Also, use of attempted movement introduced imbalances between subjects with SCI and controls related to lack of proprioceptive feedback in subjects with SCI, and the presence of a different cognitive effort underlying attempting movement when such movement does or does not occur. Movement in the four extremities was monitored visually during fMRI scanning, but subvisible muscle contractions might have occurred that could influence interpretation of motor system activation. In addition, given that numerous variables influence motor outcome and brain function after SCI (Humphrey et al. 2000; Cramer et al. 2005), results could vary in other cohorts, e.g., in subjects with more recent SCI, those with incomplete motor deficits, or those with older age.

However, the results suggest that because motor imagery training is able to modify some brain functions related to attempted movement, despite the absence of overt movements, motor imagery training might have value as a potential adjunct to restorative therapies in subjects with SCI.

**Acknowledgments** We thank Steven Kanor, PhD, of Enabling Devices (Hastings-on-Hudson, NY) for his generosity in assisting with construction of the sensor devices that digitally recorded tapping of the tongue and foot 5-part sequences. This study was supported by the Roman Reed Spinal Cord Injury Research Fund of California, and by grant M01 RR000827-29 from the U.C. Irvine General Clinical Research Centers Program of the National Center for Research Resources, National Institutes of Health.

## References

Alkadhi H, Brugger P, Boendermaker S, Crelier G, Curt A, Hepp-Reymond M, Kollias S (2005) What disconnection tells about motor imagery: evidence from paraplegic patients. Cereb Cortex 15:131–140

Brett M, Anton J-L, Valabregue R, Poline J-B (2002) Region of interest analysis using an SPM toolbox. In: 8th International conference on functional mapping of the human brain, June 2–6, 2002, Sendai, Japan

Carmena J, Lebedev M, Crist R, O'Doherty J, Santucci D, Dimitrov D, Patil P, Henriquez C, Nicolelis M (2003) Learning to control a brain–machine interface for reaching and grasping by primates. PLoS Biol 1:E42

Coren S (1993) The lateral preference inventory for measurement of handedness, footedness, eyedness, and earedness: norms for young adults. Bull Psychon Soc 31:1–3

Cramer SC, Lastra L, Lacourse MG, Cohen MJ (2005) Brain motor system function after chronic, complete spinal cord injury. Brain 128:2941–2950

Crosbie JH, McDonough SM, Gilmore DH, Wiggam MI (2004) The adjunctive role of mental practice in the rehabilitation of the upper limb after hemiplegic stroke: a pilot study. Clin Rehabil 18:60–68

Curt A, Dietz V (1999) Electrophysiological recordings in patients with spinal cord injury: significance for predicting outcome. Spinal Cord 37:157–165

Davey N, Smith H, Wells E, Maskill D, Savic G, Ellaway P, Frankel H (1998) Responses of thenar muscles to transcranial magnetic stimulation of the motor cortex in patients with incomplete spinal cord injury. J Neurol Neurosurg Psychiatry 65:80–87

Decety J, Boisson D (1990) Effect of brain and spinal cord injuries on motor imagery. Eur Arch Psychiatry Clin Neurosci 240:39–43

Dijkerman HC, Letswaart M, Johnston M, MacWalter RS (2004) Does motor imagery training improve hand function in chronic stroke patients? A pilot study. Clin Rehabil 18:538–549

Dirnberger G, Frith C, Jahanshahi M (2005) Executive dysfunction in Parkinson's disease is associated with altered pallidal-frontal processing. Neuroimage 25:588–599

Dobkin B, Havton L (2004) Basic advances and new avenues in therapy of spinal cord injury. Annu Rev Med 55:255–282

Dobkin BH, Firestine A, West M, Saremi K, Woods R (2004) Ankle dorsiflexion as an fMRI paradigm to assay motor control for walking during rehabilitation. Neuroimage 23:370–381

Doyon J, Penhune V, Ungerleider L (2003) Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. Neuropsychologia 41:252–262

Friehs G, Zerris V, Ojakangas C, Fellows M, Donoghue J (2004) Brain–machine and brain–computer interfaces. Stroke 35:2702–2705

Gerardin E, Sirigu A, Lehericy S, Poline JB, Gaymard B, Marsault C, Agid Y, Le Bihan D (2000) Partially overlapping neural networks for real and imagined hand movements. Cerebral Cortex 10:1093–1104

Humphrey D, Mao H, Schaeffer E (2000) Voluntary activation of ineffective cerebral motor areas in short- and long-term paraplegics. Soc Neurosci (abstract)

Jackson P, Lafleur M, Malouin F, Richards C, Doyon J (2003) Functional cerebral reorganization following motor sequence learning through mental practice with motor imagery. Neuroimage 20:1171–1180

Jackson PL, Doyon J, Richards CL, Malouin F (2004) The efficacy of combined physical and mental practice in the learning of a foot-sequence task after stroke: a case report. Neurorehabil Neural Repair 18:106–111

Jeannerod M, Frak V (1999) Mental imaging of motor activity in humans. Curr Opin Neurobiol 9:735–739

Johnson-Frey SH (2004) Stimulation through simulation? Motor imagery and functional reorganization in hemiplegic stroke patients. Brain Cogn 55:328–331

Jueptner M, Weiller C (1998) A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. Brain 121(Pt 8):1437–1449

Kaji R (2001) Basal ganglia as a sensory gating devise for motor control. J Med Invest 48:142–146

Lacourse M, Cohen M, Lawrence K, Romero D (1999) Cortical potentials during imagined movements in individuals with chronic spinal cord injuries. Behav Brain Res 104:73–88

Lacourse M, Orr E, Cramer S, Cohen M (2005) Brain activation during execution and motor imagery of novel and skilled sequential hand movements. Neuroimage 27:505–519

Lacourse M, Turner J, Randolph-Orr E, Schandler S, Cohen M (2004a) Cerebral and cerebellar sensorimotor plasticity following motor imagery-based mental practice of a sequential movement. J Rehabil Res Dev 41:505–524

Lacourse MG, Turner JA, Randolph-Orr E, Schandler SL, Cohen MJ (2004b) Cerebral and cerebellar sensorimotor plasticity following motor imagery-based mental practice of a sequential movement. J Rehabil Res Dev 41:505–524

Maillard L, Ishii K, Bushara K, Waldvogel D, Schulman A, Hallett M (2000) Mapping the basal ganglia: fMRI evidence for somatotopic representation of face, hand, and foot. Neurology 55:377–383

Milliken G, Stokic D, Tarkka I (1999) Sources of movement-related cortical potentials derived from foot, finger, and mouth movements. J Clin Neurophysiol 16:361–372

Oldfield R (1971) The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 9:97–113

Page S, Levine P, Sisto S, Johnston M (2001) Mental practice combined with physical practice for upper-limb motor deficit in subacute stroke. Phys Ther 81:1455–1462

Page SJ, Levine P, Leonard AC (2005) Effects of mental practice on affected limb use and function in chronic stroke. Arch Phys Med Rehabil 86:399–402

Pascual-Leone A, Nguyet D, Cohen L, Brasil-Neto J, Cammarota A, Hallett M (1995) Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. J Neurophysiol 74:1037–1045

Pomeroy V, Clark C, Miller J, Baron J, Markus H, Tallis R (2005) The potential for utilizing the "mirror neurone system" to enhance recovery of the severely affected upper limb early after stroke: a review and hypothesis. Neurorehabil Neural Repair 19:4–13

Porro C, Francescato M, Cettolo V, Diamond M, Baraldi P, Zuiani C, Bazzocchi M, di Prampero P (1996) Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. J Neurosci 16:7688–7698

Raineteau O, Fouad K, Bareyre F, Schwab M (2002) Reorganization of descending motor tracts in the rat spinal cord. Eur J Neurosci 16:1761–1771

Sabbah P, de Schonen S, Leveque C, Gay S, Pfefer F, Nioche C, Sarrazin J, Barouti H, Tadie M, Cordoliani Y (2002) Sensorimotor cortical activity in patients with complete spinal cord injury: a functional magnetic resonance imaging study. J Neurotrauma 19:53–60

Scherberger H, Jarvis MR, Andersen RA (2005) Cortical local field potential encodes movement intentions in the posterior parietal cortex. Neuron 46:347–354

Scholz V, Flaherty A, Kraft E, Keltner J, Kwong K, Chen Y, Rosen B, Jenkins B (2000) Laterality, somatotopy and reproducibility of the basal ganglia and motor cortex during motor tasks. Brain Res 879:204–215

Sharma N, Pomeroy VM, Baron JC (2006) Motor imagery: a backdoor to the motor system after stroke? Stroke 37:1941–1952

Toda H, Hamani C, Lozano A (2004) Deep brain stimulation in the treatment of dyskinesia and dystonia. Neurosurg Focus 17:E2

Topka H, Cohen L, Cole R, Hallett M (1991) Reorganization of corticospinal pathways following spinal cord injury. Neurology 41:1276–1283

Vaillancourt DE, Mayka MA, Thulborn KR, Corcos DM (2004) Subthalamic nucleus and internal globus pallidus scale with the rate of change of force production in humans. Neuroimage 23:175–186