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NEUROSYSTEMS

# Sensorimotor training promotes functional recovery and somatosensory cortical map reactivation following cervical spinal cord injury

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## Abstract

Sensorimotor activity has been shown to play a key role in functional recovery after partial spinal cord injury (SCI). Most studies in rodents have focused on the rehabilitation of hindlimb locomotor functions after thoracic or lumbar SCI, whereas forelimb motor and somatosensory abilities after cervical SCI remain largely uninvestigated, despite the high incidence of such injuries in humans. Moreover, little is known about the neurophysiological substrates of training-induced recovery in supraspinal structures. This study was aimed at evaluating the effects of a training procedure combining both motor and sensory stimulation on behavioral performance and somatosensory cortical map remodeling after cervical (C4–C5) spinal hemisection in rats. This SCI severely impaired both sensory and motor capacities in the ipsilateral limbs. Without training, post-lesion motor capacities gradually improved, whereas forepaw tactile abilities remained impaired. Consistently, no stimulus-evoked responses were recorded within the forepaw representational zone in the primary somatosensory (S1) cortex at 2 months after the SCI. However, our data reveal that with training started from the 7th day post-lesion, a nearly complete recovery (characterized by an early and rapid improvement of motor functions) was associated with a gradual compensation of tactile deficits. Furthermore, the recovery of tactile abilities was correlated with the areal extent of reactivation of S1 cortex forepaw representations. Rehabilitative training promoted post-lesion adaptive plasticity, probably by enhancing endogenous activity within spared spinal and supraspinal circuits and pathways sustaining sensory and motor functions. This study highlights the beneficial effect of sensorimotor training in motor improvement and its critical influence on tactile recovery after SCI.

## Introduction

Spinal cord injuries (SCIs) in humans result in a variety of sensorimotor impairments. The majority of SCIs occur at cervical levels (Jackson *et al.*, 2004) and most of these are rather 'incomplete' (Raineteau & Schwab, 2001). It is now well established that the central nervous system is capable of substantial reorganization in cases of incomplete SCI, as cortical, subcortical and much of the local spinal cord circuitry remains intact and partially interconnected through spared axonal pathways (Raineteau & Schwab, 2001). In view of such a potential of neuroplasticity, a variety of techniques employing pharmacological (Chau *et al.*, 1998a,b) or sensorimotor stimulation (Lynskey *et al.*, 2008) have been developed to promote functional recovery. In addition to the influence of the location and severity of SCI, the rehabilitative strategies that reinforced sensory experience associated with motor practice, in particular through imposed exercise, were shown to substantially improve sensorimotor recovery following SCI (for reviews, see Rossignol *et al.*, 2006, 2008; Multon *et al.*, 2003; Hutchinson *et al.*, 2004; Smith *et al.*, 2006; Goldshmit *et al.*, 2008). However, none of these studies have investigated the effects of post-lesion training on the recovery of tactile abilities.

Rehabilitative strategies have been hypothesized to enhance activity within the residual neuronal networks and thus promote adaptive neuroplasticity mechanisms (Edgerton *et al.*, 2001; Lynskey *et al.*, 2008, Barrière *et al.*, 2008). Optimal rehabilitative strategies should not be limited to targeting activity-dependent spinal cord plasticity below the site of injury but should involve all levels of the sensorimotor pathways (Florence *et al.*, 2001; Beekhuizen & Field-Fote, 2005; Thomas & Gorassini, 2005; Winchester *et al.*, 2005; for a review, see Adkins *et al.*, 2006; Girgis *et al.*, 2007; Hoffman & Field-Fote, 2007; Nishimura *et al.*, 2007). However, the neural substrates of reorganization in supraspinal structures after SCI and their functional correlates remain poorly understood. After cervical SCI, the deprived sectors of the primary somatosensory (S1) maps were not found to regain evoked responses in untrained rats and monkeys (Jain *et al.*, 1995, 1997). However, as it has been shown that adaptive experience-dependent remodeling of somatosensory and motor maps in primary cortical areas parallels functional recovery after cortical injuries (Nudo & Milliken, 1996; Xerri *et al.*, 1999), the question arises as to whether sensorimotor training would drive S1 cortical changes after SCI and impact tactile abilities.

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The present study, combining electrophysiological cortical mapping and behavioral tests, was aimed at gaining insight into the influence of locomotor training on the restoration of tactile and sensorimotor abilities in relation to remodeling of S1 cortex representation after cervical spinal hemisection.

## Materials and methods

All experiments were carried out in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals [NIH Publication no. 80-23; revised in 1996 for the UK Animals (Scientific Procedures) Act 1986] and associated guidelines or with the Policy on Ethics approved by the Society for Neuroscience in November 1989 and amended in November 1993. All efforts were made to minimize the number of animals used.

### *Experimental design*

After an initial period devoted to familiarizing the animals with the behavioral testing conditions, the rats were subjected to the unilateral SCI. The lesion extent was routinely assessed by *in vivo* anatomical magnetic resonance imaging (MRI). After a 4 day period, the behavioral testing was initiated and repeated once per week for 2 months. At completion of behavioral testing, cortical mapping was performed. The animals were then killed and the cervical spinal cord was removed for subsequent histological controls.

### *Experimental groups*

Three-month-old male Wistar rats ($n$ = 33) weighing between 350 and 400 g were used in this study. Both behavioral and electrophysiological mapping experiments were carried out on three groups: sham-operated (Sh) ($n$ = 7), lesioned (L) ($n$ = 11) and lesioned trained (LT) ($n$ = 10) rats. In the LT rats, cortical mapping was performed at either 30 ($n$ = 2) or 60 ($n$ = 8) days after SCI. An additional group of rats was used for preliminary electrophysiological and anatomical assessment of the SCI (validation group, $n$ = 5).

### *Spinal cord hemisection*

Anesthesia was induced with an intramuscular injection of ketamine (25 mg/kg, Ketalar®, Virbac, France) and medetomidine (0.25 mg/kg, Domitor®, Orion Pharma, Finland). An analgesic substance, butorphanol tartrate (0.05 mg/kg, s.c., Torbugesic® 1%, Fort Dodge Animal Health LTD, IA, USA), was injected at 15 min before surgery. The core temperature was monitored continuously by rectal thermistor probe and maintained at between 37 and 38°C with a feedback-controlled homeothermic blanket system (Harvard Apparatus Ltd, Kent, UK).

After a medial skin incision along the dorsal part of the neck, the skin and superficial muscles were retracted. The paravertebral muscles inserting on the dorsal aspect of the C4 vertebrae were dissected and a bilateral laminectomy exposed the dorsal surface of the spinal cord. The dura was incised and droplets of Lidocaine (Xylovet®, CEVA, France) were applied to the spinal cord to decrease spinal reflexes. In both the L and LT groups, a hemisection of the left spinal cord was performed using microscissors under microscope visualization. The Sh rats underwent the surgical procedure described above but the spinal cord was not damaged. After the surgery, a local antibiotic was applied on the exposed part of the spinal cord (Flumiquil® 3%, CEVA) and the removed vertebral plate was replaced and secured with dental cement. The muscles and skin were sutured using absorbable and non-absorbable materials, respectively. The rats were allowed to recover in warmed cages where water and food were easily accessible.

Over the first 4 post-operative days (throughout the period of sensitive pain), each animal received a subcutaneous injection of lactate ringer (10 mL) complemented by butorphanol tartrate (0.05 mg/kg) every 3 h. Thereafter, paracetamol (300 mg/kg) codeine (60 mg/kg) effervescent pills (paracetamol/codeine, 500 mg/30 mg, Teva®, TEVA Classics) were mixed into the animal's drinking bottle until signs of pain disappeared.

### *Functional and anatomical validation of the spinal cord injury*

#### *Electrophysiological cortical recordings*

Validation of the spinal cord hemisection between the C4 and C5 segments was performed in the validation group by assessment of evoked activity within the forepaw area of the contralateral S1 cortex. Electrophysiological multiunit recordings and receptive field (RF) mapping were used to reconstruct the forepaw representation in layer IV, before and at 1 h after the lesion was induced (see Electrophysiological mapping procedures below). Post-lesion recordings did not reveal any somatosensory stimulus-evoked activity within the ipsilateral forepaw cortical area in response to somatosensory stimulation of the contralateral or even ipsilateral forepaws.

#### *In-vivo anatomical magnetic resonance imaging of the spinal cord*

The location and completeness of the spinal cord hemisection were assessed with anatomical MRI in each rat in order to immediately discard from our longitudinal study rats with incomplete spinal cord hemisection or with lesions extending beyond the midline. In this study, 70% of the rats subjected to the SCI were included. All MRI acquisitions were performed immediately after surgery with a BRUKER Pharmascan spectrometer (7 Tesla magnet with a 16 cm horizontal bore size) using a dedicated transmit/receive rat body coil (linear birdcage coil of inner diameter 62 mm). During acquisition, the animal's respiration was monitored and body temperature was maintained between 37 and 38°C with a heating blanket. To minimize motion artifacts, image acquisition was triggered on the animal's respiratory cycle. Horizontal and coronal contiguous T2*-weighted slices centered at the lesion site were acquired using gradient-echo sequences (for horizontal slices: FLASH 2D sequence with TR/TE, 300/3.4 ms; flip angle, 30°; field of view, 40 mm; matrix size, 256 × 256; slice thickness, 600 $\mu$m and four averages; for coronal slices: FLASH 3D sequence with TR/TE, 100/4.2 ms; flip angle, 15°; field of view, 40 × 40 × 0.5 mm$^3$; matrix size, 256 × 192 × 16 and three averages) (Fig. 1A and B).

#### *Histological controls*

At either 30 or 60 days after SCI, animals were given a lethal dose of pentobarbital sodium (150 mg/kg, i.p., CEVA) and transcardially perfused with 100 mL cold saline followed by 500 mL of freshly prepared cold 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). A piece of 10 mm spinal cord segment between C3 and C6 was carefully dissected out and post-fixed for 12 h at 4°C in 4% paraformaldehyde. The blocks were cryoprotected by successive transfers into increasing concentrations (10, 20 and 30%) of sucrose solution in 0.1 M phosphate buffer for 72 h at 4°C. For histological examination, the spinal cord was frozen using carbon dioxide and 40-$\mu$m-thick coronal sections of a spinal cord segment of 3 mm

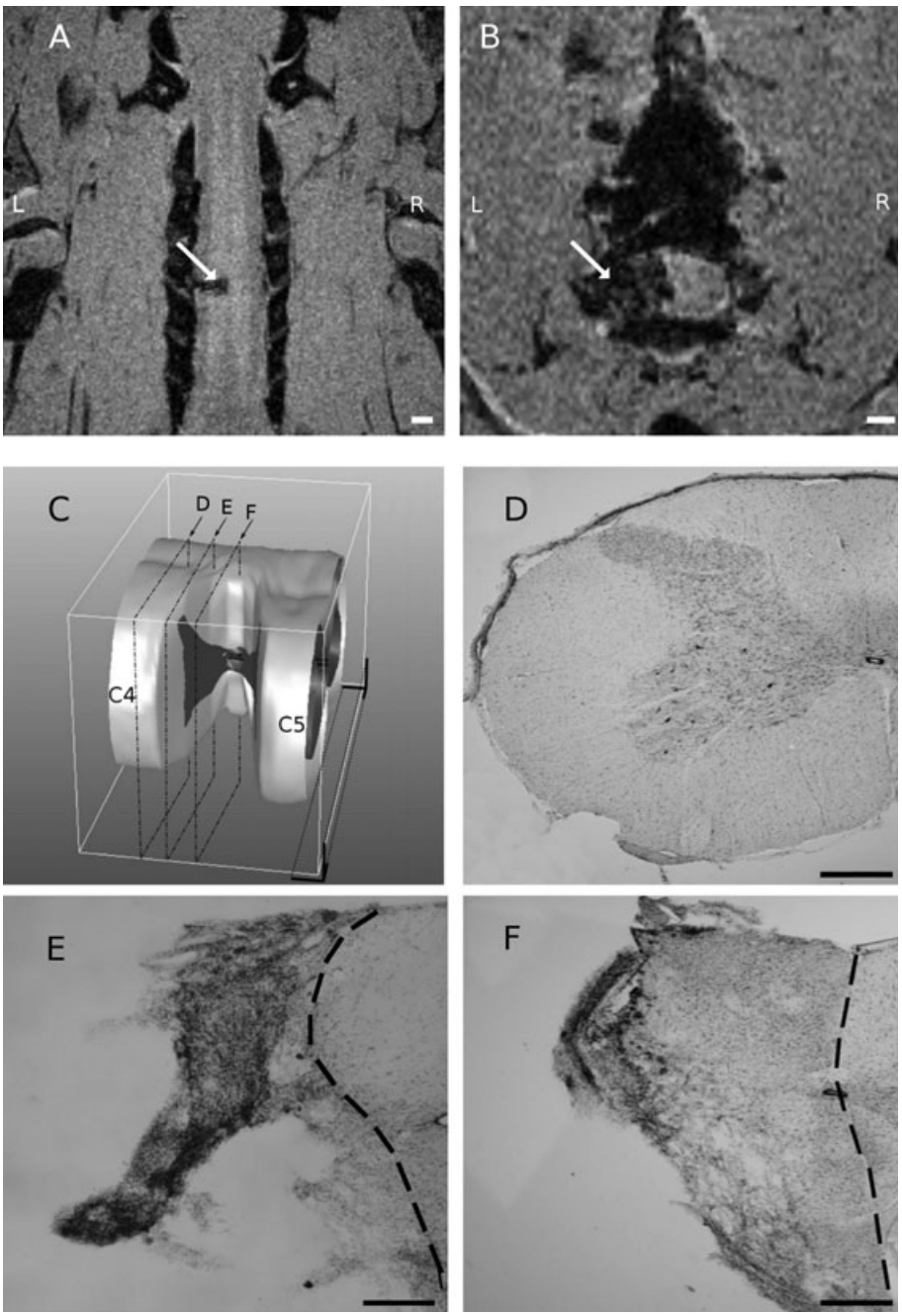


FIG. 1. SCI evaluation. (A and B) *In-vivo* MRI T2*-weighted images at 7 T of the spinal cord after hemisection between segments C4 and C5. (A) Horizontal and (B) coronal slices through the cervical spinal cord (for horizontal slices: FLASH 2D sequence with TR/TE, 300/3.4 ms; flip angle, 30°; field of view, 40 mm; matrix size, 256 × 256; slice thickness, 600 $\mu$m and four averages; for coronal slices: FLASH 3D sequence with TR/TE, 100/4.2 ms; flip angle, 15°; field of view, 40 × 40 × 0.5 $mm^3$; matrix size, 256 × 192 × 16 and three averages). The white arrows point to the hemisection. R, right; L, left. Morphological illustrations of the C4-C5 hemisection. (C) Three-dimensional reconstruction showing the extent of the lesion in the cervical spinal cord segment. (D and E) Microphotographs of coronal sections corresponding to the section planes illustrated in C and stained with cresyl violet. Dashed lines in E and F delineate the limits between intact and damaged neural tissue. Scale bars: 1 mm (A and B), 500 $\mu$m (C–F).

centered on the lesion were taken using a cryostat. Every sixth section was mounted on a slide and then stained with cresyl violet (Fig. 1D–F). Sections were digitally imaged and analyzed for an unbiased stereological estimation of tissue volume loss at 1 and 2 months after the lesion by the Cavalieri method using Mercator software (Explora Nova, France). The coefficient of error was also determined for each volume estimate. Section images were also processed with free-D software (Andrey & Maurin, 2005) to reconstruct a three-dimensional model of the lesion site. Based on this second anatomical validation of the lesion extent, animals with incomplete hemisection were discarded from the study.

### *Electrophysiological mapping procedures*

The mapping procedure used in the present study was described in detail previously (Coq & Xerri, 1998; Rosselet *et al.*, 2006). Anesthesia was induced with an initial intramuscular injection of ketamine (25 mg/kg) and medetomidine (0.25 mg/kg), and rats were maintained at an

areflexive level of anesthesia throughout the experiment by supplemental half-doses of anesthetic. The core temperature was monitored continuously by rectal thermistor probe and maintained between 37 and 38°C with a heating pad. The head was placed in a stereotaxic frame. To prevent cerebral oedema, cerebrospinal fluid was first drained through an opening in the dura covering the cisterna magna, after resection of posterior neck muscles. A craniotomy (about 16 $mm^2$) was then made to expose the S1 cortical forepaw area and the dura was incised and resected. The cortical surface was bathed in a thin layer of warm silicone fluid to prevent drying. Magnified images of the exposed parietal cortex and the ventral and dorsal surfaces of the forepaw contralateral to the cerebral hemisphere of interest were imaged with a high-resolution camera mounted on an operating microscope. Locations of microelectrode penetrations relative to the vasculature of the cortical surface and boundaries of cutaneous RFs were recorded on the digitized images of the cortex and forepaw, respectively, using Map 0.925 software (Peterson & Merzenich, 1995). Small clusters of neurons (two to four) were recorded with parylene-coated tungsten microelectrodes (about 1 MΩ at 1 kHz; WPI, UK). The electrode was moved perpendicular to the cortical surface in cartesian coordinates by a three-dimensional stepping micromanipulator (Märzhauser, FST, Canada) and a zero level was set using the recording artifact generated by the microelectrode contact with the cortical surface. Responses from neurons in layer IV were recorded at a depth of approximately 650–700 $\mu$m and the interelectrode penetration distance averaged 100 $\mu$m in all groups of rats. The amplitude of the background noise usually ranged from 15 to 20 mV with a signal-to-noise ratio varying from 4 to 6. The multiunit signal was amplified, filtered (bandwidth, 0.5–5 kHz) and displayed on an oscilloscope. This signal was further rectified, passed through a discriminator (the output of which was proportional to the part of the input signal just above the noise floor) and output to an audio monitor.

At each recording site, bursts of activity elicited by natural stimulation allowed us to classify neuronal responses as cutaneous or non-cutaneous. The cutaneous RFs of small clusters of neurons were defined for each cortical recording site as the area of skin where just-visible skin indentation or hair deflection elicited reliable changes in multiple-unit discharge. This stimulation was produced with a fine-tipped, hand-held glass probe and monitored with 4 × magnifying glasses. Responses evoked by nail movements, also classified as cutaneous responses, were examined while the tips of the digits were maintained firmly in place to minimize joint movement and skin deformation. Non-cutaneous responses were identified by taps and pressure on tendons, intrinsic muscle or joint manipulations where no cutaneous response was found. Cortical sites exhibiting only spontaneous discharges were classified as unresponsive.

We used Canvas software (Deneba) to elaborate maps of the forepaw representation by drawing boundaries around cortical sites whose RFs were restricted to a common forepaw subdivision, i.e. finger, palmar and pad. Borders were drawn midway between adjacent recording sites where RFs were located on distinct and separate skin subdivisions. A boundary line crossed cortical sites at which a single RF included different but adjoining skin subdivisions of the forepaw. The same principle was used to draw boundaries encompassing cortical sites where non-cutaneous responses were obtained for each forepaw subdivison. Canvas software was further applied to calculate the area of each cutaneous and non-cutaneous region of the cortical somatosensory map.

## Behavioral tests

To minimize the effects of stress during repeated post-operative testing, animals were daily familiarized, for about 1 h, with all of the behavioral tasks used during testing, for 2 weeks prior to surgery. Behavioral testing was then conducted over an 8 week period after surgery (on the 4th and 7th post-operative days, then once per week). Testing was systematically performed before training in LT rats.

### *Open-field test*

The forelimb and hindlimb locomotor deficits were assessed during spontaneous locomotion using an open-field scoring derived from the Bass, Beattie and Bresnahan scale and designed for an accurate evaluation of the behavioral consequences of cervical SCI (Martinez *et al.*, 2009). Rats were tested in pairs for a 4 min period in a circular Plexiglas arena (95 cm diameter, 40 cm wall height) with an anti-skid floor. These open-field sessions were recorded in high-quality digital video for off-line analysis with camcorders (Sony HDR-HC3E) set to night-shot mode and from different perspectives using both wide fields and zoom shots. The videos were analyzed at normal speed and in slow-motion by teams of two examiners, who consulted with one another to complete a scoring grid that gave a forelimb and hindlimb functional score to each animal in each session. Behavioral deficits affecting the limbs ipsilateral to the cervical SCI were categorized by evaluating the articular movement amplitude, weight support, fine distal positioning and stepping abilities. The scaling grid yielded final scores (maximum grade, 20) for the affected forelimb and hindlimb.

### *Horizontal ladder-walking test*

Locomotor deficits were further assessed using the ladder rung-walking test apparatus (Soblosky *et al.*, 1997). Animals were trained to walk on a ladder (200 cm long; rungs of 3 mm diameter spaced by 2 cm) from a lighted box to a dark box. A mirror was positioned at 45° under the ladder to facilitate video recording of paw movement and positioning from lateral and ventral views of the paws. The pre-lesion training period for each rat lasted until less than two foot faults were made when traversing the ladder. A neurological score ranging from 1 to 8 (Soblosky *et al.*, 1996) characterized the rat's ability to cross the ladder using the affected forepaws and hindpaws on the ladder rungs. For example, 3 points were assigned when the animal was unable to traverse but placed both the affected hindpaw and forepaw on the horizontal surface rungs of the ladder and maintained body balance for at least 5 s; 6 points were assigned when the rat successfully traversed the ladder but was unable to place both affected paws on the rungs (for more details, see Soblosky *et al.*, 1996).

### *Ladder-climbing test*

Upper limb motor function was assessed using a modified version of the procedure described by Li *et al.* (2003). Rats were allowed to climb twice up a ladder of 1 m length inclined at an angle of 45°. Forepaw faults were scored with slow-motion video analysis and each paw placement was assigned a score ranging from 0 to 2, with a score of 2 attributed for a correct paw placement, 1 when paw placement was delayed or overshot the ladder rung through the grid to the level of the wrist, and 0 when the paw overshot through the grid to the level of the elbow or axilla. An asymmetry index (AI) was then calculated by comparing the scores for affected and unaffected forelimbs averaged for over 10 consecutive placements: AI = [average score (affected) − average (unaffected)]/[average score (affected) + average (unaffected)]. An AI of < 0 indicated a functional deficit of the forelimb ipsilateral to the spinal lesion.

### *Adhesive removal test*

The magnitude of asymmetry in somatosensory sensitivity was evaluated by using the bilateral tactile stimulation test (Schallert *et al.*, 1982, 1983, 2000). With animals placed in a cage without

bedding, one strip of adhesive tape (5 × 5 mm) was applied on the plantar surface of each forepaw and the time to remove each strip was measured (to a maximum of 5 min). Animals were tested five times per session with 10 min between trials and the order of adhesive placement (left or right paw) was alternated between consecutive trials. An AI score was then calculated using averaged times for each paw, such that AI = average removal time (affected paw)/[average time (affected paw) + average time (unaffected paw)]. An AI of > 0.5 was indicative of a somatosensory deficit in the paw ipsilateral to the spinal lesion.

### *Post-injury training procedure*

After SCI, rats were randomly assigned to the trained (LT) or untrained (L) groups. All rats were housed under standard laboratory conditions. LT rats were subjected to locomotion imposed by an original device consisting of a carrousel including six individual boxes, the rotation speed of which was constant (linear speed, 8 m/min.). The animals walked on carpets of different textures and roughnesses (Fig. 2). The training was performed from the 7th to the 30th or 60th day after the lesion and consisted of two sessions of 30 min per day, 5 days per week. The practical advantage of this original training device was to simultaneously provide several animals with similar sensorimotor stimulation regimens while providing them with a variety of tactile stimuli.

### *Statistical analyses*

All statistical analyses were performed using Statistica 8.0 software (StatSoft, Tulsa, OK, USA). For the behavioral tests, ANOVA was used to evaluate the effects of experimental groups and post-operative time.

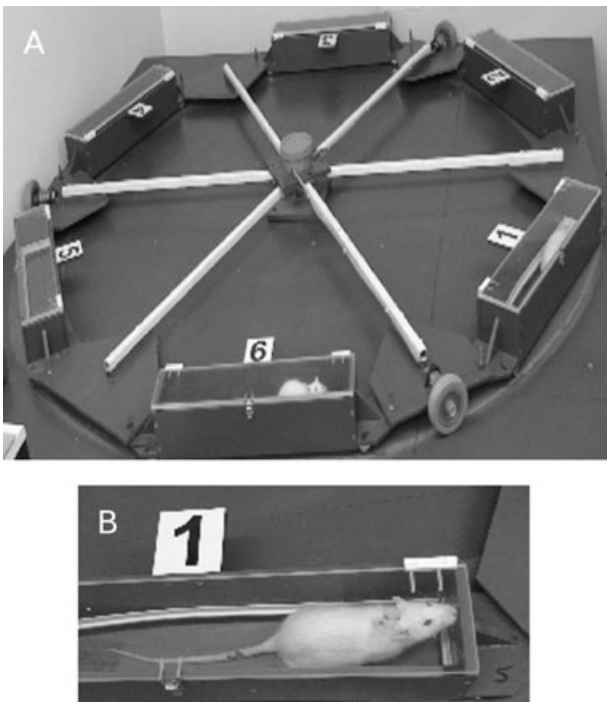


FIG. 2. Automatic training carousel. (A) Photograph of the automatic training device (linear speed: 8 m/min) used in the LT group. (B) Box in which individual rats were gently incited to walk on a tactile carpeted floor covered with pieces of paint-coated sandpaper with various roughnesses.

ANOVA was supplemented with multiple comparisons (Newman-Keul *post-hoc* test). A *t*-test was also used to compare the L and LT with Sh groups. Mann–Whitney *U* and Chi-squared tests were used to compare the cortical map data of the different groups. A $P$ value of $< 0.05$ was considered statistically significant. Results are presented as means ± confidence limits at $P = 0.05$.

## Results

### *Extent of the spinal cord lesions*

No intraspinal tissue damage was detected in Sh rats. In the L and LT groups, in which animals were initially included on the basis of MRI analysis (Fig. 1A and B), the tissue damage assessed at 1 or 2 months following the hemisection was restricted to the side ipsilateral to the injury (Fig. 1E and F). No significant difference in the mean volumes of tissue loss was found between the L (6.01 ± 0.30 $mm^3$) and LT (5.77 ± 0.35 $mm^3$) group (*t*-test, $P = 0.17$, n.s.).

### *Behavioral assessment*

#### *Spontaneous recovery profile of sensorimotor capacities in the untrained rats*

We employed the battery of behavioral tests described above to evaluate the spontaneous recovery of sensorimotor abilities after cervical spinal cord hemisection. The sensorimotor capacities of the SCI rats from the L group were tested in the context of voluntary locomotion on a flat surface (open-field), in conditions requiring sensorimotor skills with rungs (walking on horizontal ladders and climbing inclined ladders) and forepaw tactile sensitivity (adhesive removal test). ANOVA yielded a significant effect of post-operative delay for all tests except adhesive removal (open-field: forelimb, $F_{8,78} = 28.29$; hindlimb, $F_{8,78} = 4.88$; climbing: $F_{8,78} = 18$; ladder walking: $F_{8,78} = 11.42$; all $P < 0.001$; adhesive removal: $F_{8,78} = 0.77$, $P = 0.63$, n.s.), indicating that substantial motor recovery occurred in the L rats during the two post-operative months.

For the first 2–3 days following lesion, the primary consequence of the hemisection was a forelimb and hindlimb flaccid paresis ipsilateral to the lesion, resulting in a lack of postural support. Following this initial 2–3 days, the hindlimb motor performance of rats in the L group rapidly improved until 2 weeks post-lesion, from a mean hindlimb score in the open-field of 10.27 ± 3.80 on day 4 to a score of 14.45 ± 2.75 on day 14 ($P < 0.05$, Fig. 3A). For the remainder of the observation period, L rats showed a steady, continuous increase in the amplitude of hindlimb articular movements, which was first associated with an improvement in body-weight support in stationary states and later with displacements in the open-field. Following these improvements, partial stepping showed some recovery, whereas anteroposterior coordination remained impaired due to enduring forepaw deficits.

In contrast to the observed hindlimb improvements, L rats exhibited severe impairment of forelimb movements during the first post-operative week. Slight proximal joint movements were observed in open-field (forelimb score on day 7: 1.27 ± 0.28), whereas distal joint movements were absent in all rats. During the same period, performance on ladder tests showed that rats had great difficulty in placing their affected forepaws on rungs of both horizontal (score: 2.72 ± 0.86, Fig. 3D) and inclined (score: −1 ± 0, Fig. 3C) ladders, whereas in these same tests, the ipsilateral hindlimb had recovered a propulsive function during ladder traversing. Subsequent to the first week, forelimb performance gradually improved over the period between the 7th and 35th days after lesion on all three tests (day 35:

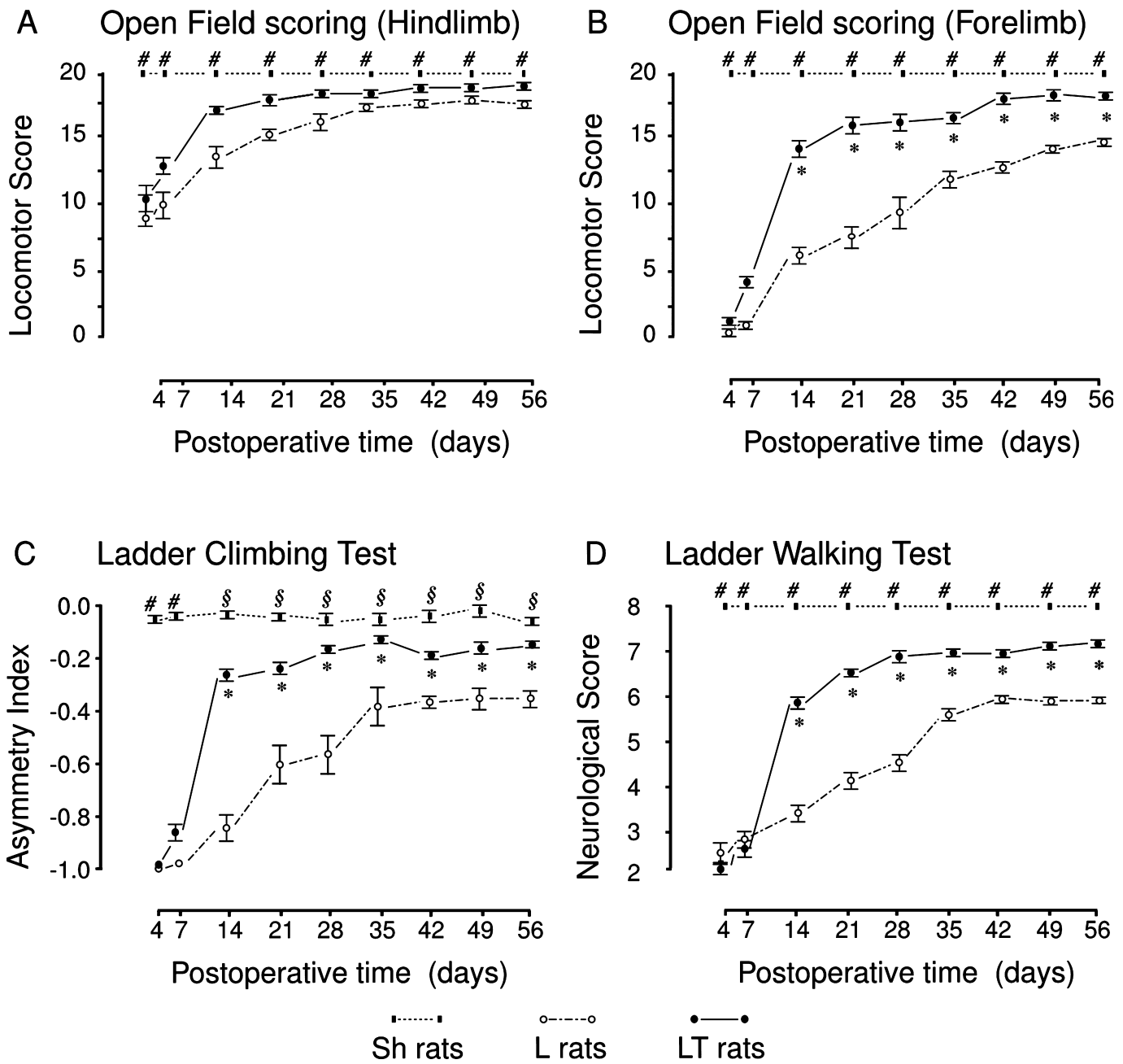


FIG. 3. Post-operative time-course of changes in sensorimotor abilities, assessed in the Sh, L and LT groups, using scoring in open-field, ladder-walking and climbing tests. (A and B) Recovery of hindlimb and forelimb locomotor capacities as scored in open-field conditions. The L and LT group hindlimb motor performances improved rapidly during the first 2 weeks ($P < 0.05$) and then remained stable. These two groups exhibited similar performances over the entire post-operative period, at the end of which only the LT rats exhibited scores that did not differ from those of the Sh rats. (B and C) Initial forelimb deficits, assessed with open-field and climbing tests, were similar in the L and LT rats during the first two post-lesion weeks. LT group sensorimotor capacities were significantly better than those of the L group from the 14th post-lesion day ($P < 0.00005$). (D) The ladder-walking scores confirmed this finding. In the open-field forelimb and ladder-walking tests, neither the L nor LT rats regained the Sh scores ($P < 0.0001$). In contrast, only the climbing test scores of the LT rats reached those of the Sh rats from the 14th day. Statistical differences: $^{\#}$Sh vs. L and LT rats, *L vs. LT rats, and $^{\S}$Sh vs. L rats.

mean open-field forelimb, 11.75 ± 1.78; ladder-walking test, 5.5 ± 0.32; ladder-climbing test, −0.33 ± 0.17; $P < 0.00005$) and reached a plateau during the second post-operative month (Fig. 3B–D). This recovery remained incomplete, however, as indicated by significantly lower scores in the L group compared with the Sh rats ($P < 0.0001$) at the completion of the post-operative testing period (Fig. 3). We observed residual deficits in paw orientation during the swing phase of stepping, a persistent loss of digit tonicity, jerky forelimb movements and inconsistent anteroposterior coordination during locomotion in the open-field. Moreover, deficits in paw placement and grasping abilities (as assessed by horizontal and inclined ladder tests) persisted throughout the testing period.

Despite the spontaneous recovery of motor capacities, L rats showed no improvement in tactile abilities on the adhesive removal test between days 4 and 56 post-lesion (mean AI: 0.95 ± 0.04 and 0.97 ± 0.02, respectively; $P = 0.99$, n.s.; Fig. 4). These deficits were

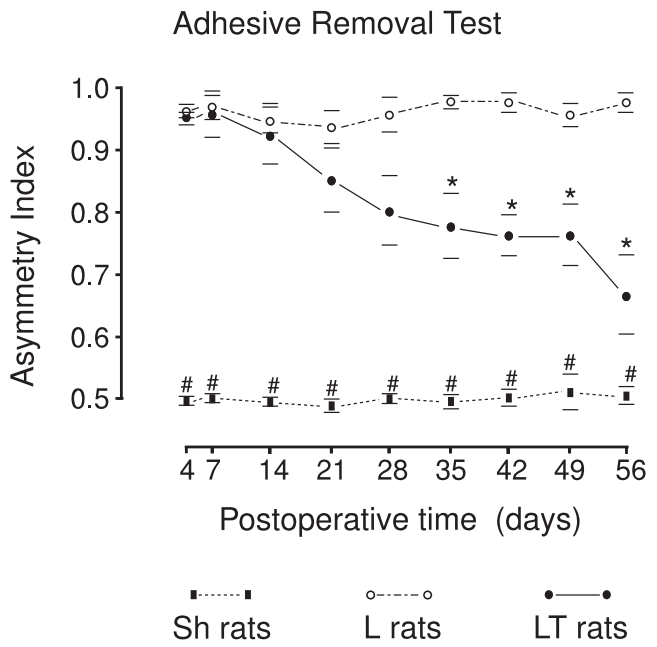


FIG. 4. Post-operative time-course of tactile abilities in the Sh, L and LT groups as assessed by the adhesive removal test. The L rats did not show any improvement in tactile abilities over the 2 month post-lesion period. In contrast, the tactile scores of the LT rats gradually improved between the 4th and 56th days ($P < 0.00002$). From the 35th day, the LT rats exhibited a partial recovery of tactile abilities compared with the L rats ($P < 0.0001$). Nevertheless, the scores of the LT rats remained lower than those of the Sh group, regardless of post-lesion time ($P < 0.005$). Statistical comparisons are as in Fig. 3.

found to affect only the forepaw ipsilateral to the SCI (mean removal time on day 56: 224.26 ± 65 s), as the adhesive removal times recorded for the contralateral forelimb on day 56 were similar to those of the Sh group (mean removal time: L group, 6.13 ± 2.60 s; Sh group, 5.86 ± 1.82 s).

### *Consequences of training on recovery of sensorimotor capacities after cervical hemisection*

Before the beginning of training in the LT rats, the L and LT groups exhibited similar behavioral performances. Training was initiated from the 7th day post-lesion. Rats displayed various strategies in order not to use the affected forelimb for the first few days of the training period. For example, the animal would push against the box walls with its hindlimbs while hopping in with the intact forelimb. However, all rats were found to use a quadrupedal locomotion over subsequent training sessions, which turned out to result in an improvement on the sensorimotor abilities assessed using the open-field and ladder tests, as early as day 14. An ANOVA comparing the L and LT groups yielded significant main effects of group and delay and a significant interaction between these two variables (Table 1). Interestingly, the LT rats showed a substantially greater improvement in their motor capacities than group L by day 14, which is indicated by an improvement over the first week of training (day 7 vs. 14; mean scores in open-field: forelimb, 3.8 ± 1.04 vs. 13.8 ± 1.33; ladder-climbing test: −0.83 ± 0.14 vs. −0.21 ± 0.05; ladder-walking test: 2.6 ± 0.71 vs. 5.8 ± 0.51; $P < 0.00005$ for each test) (Fig. 3B–D). However, hindlimb scores in the open-field did not show significant improvement over the same period (14.1 ± 1.89 vs. 17.5 ± 0.42) (Fig. 3A).

The motor capacities of the LT rats differed significantly from those of the L rats beginning on the 14th post-operative day (mean scores in open-field, LT vs. L respectively: forelimb, 13.80 ± 1.33 vs. 5.90 ± 2.19; ladder-climbing test: −0.21 ± 0.05 vs. −0.81 ± 0.15; ladder-walking test: 5.80 ± 0.51 vs. 3.30 ± 0.84; $P < 0.00005$ for each test) (Fig. 3B–D). Contrary to the L group, which showed a continuous but incomplete recovery of motor capacities during the first post-operative month, the LT rats regained a rapid and high level of performance over the same period through a sequence of behavioral progress similar to that of the L rats. This precocious improvement in motor capacities was then followed by a period during which performances did not increase significantly. Despite the conspicuous recovery noted in LT rats, forelimb open-field (day 56: 17.75 ± 0.72, Fig. 3B) and ladder-walking (day 56: 7.12 ± 0.23, Fig. 3D) scores in this group remained significantly lower than those of the Sh group ($P < 0.0001$). Deficits in anteroposterior coordination persisted in the LT rats until the end of testing, whereas mean scores for ladder climbing (day 56: 19.37 ± 0.36, Fig. 3C) and hindlimb open-field performances (day 56: -0.14 ± 0.04, Fig. 3A) did not differ significantly from those of the Sh rats.

The LT rats showed a more gradual improvement of their tactile abilities than their motor capacities, as illustrated by changes in the scores on the adhesive removal test from day 4 to 56 (AI: 0.94 ± 0.04 and 0.67 ± 0.09, respectively; $P < 0.00002$) (Fig. 4). The performance of the LT and L groups differed from the end of the first month onward (day 28, AI for LT and L groups: 0.80 ± 0.09 and 0.95 ± 0.04, respectively; $P < 0.0001$). Despite this substantial recovery of tactile abilities, LT rats exhibited deficits relative to the Sh group even at 2 months after lesion (AI for LT and Sh groups on day 56: 0.67 ± 0.09 and 0.51 ± 0.03, respectively; $P < 0.005$).

### *Effect of sensorimotor training on primary somatosensory forepaw representation*

Electrophysiological recordings performed at 1 or 2 months after SCI in the contralateral S1 cortex showed no supraliminar stimulus-evoked responses within the forelimb area of the L group, as was found during the first hours after the lesion. Only spontaneous, often bursting, discharges were observed, whereas evoked neuronal responses from chin and shoulder stimulation were recorded along the lateral and caudal margins of the forepaw map area, respectively. Interestingly, the representational zone for chin skin surfaces was found to expand within the cortical zone devoted to the cutaneous forepaw representation at 1 or 2 months after the SCI (Fig. 5A and B).

TABLE 1. ANOVA summary table for the main effects of group and post-lesion time, and interactions between group and post-lesion time

| | Group | Post-lesion time | Group × post-lesion time |
|---|---|---|---|
| Open-field test forelimb | $F_{1,151} = 181.49$ ($P < 0.00001$) | $F_{8,151} = 104.01$ ($P < 0.00001$) | $F_{8,151} = 5.75$ ($P < 0.00001$) |
| Open-field test hindlimb | $F_{1,151} = 18.48$ ($P < 0.00005$) | $F_{8,151} = 13.89$ ($P < 0.00001$) | $F_{8,151} = 0.332$ ($P > 0.05$; n.s.) |
| Climbing test | $F_{2,204} = 240.98$ ($P < 0.001$) | $F_{8,204} = 45.77$ ($P < 0.001$) | $F_{16,204} = 13.34$ ($P < 0.001$) |
| Ladder-walking test | $F_{1,151} = 72.22$ ($P < 0.00001$) | $F_{8,151} = 47.27$ ($P < 0.00001$) | $F_{8,151} = 5.28$ ($P < 0.00001$) |
| Adhesive removal test | $F_{2,205} = 62.07$ ($P < 0.00001$) | $F_{8,205} = 5.03$ ($P < 0.00001$) | $F_{16,205} = 6.60$ ($P < 0.00001$) |

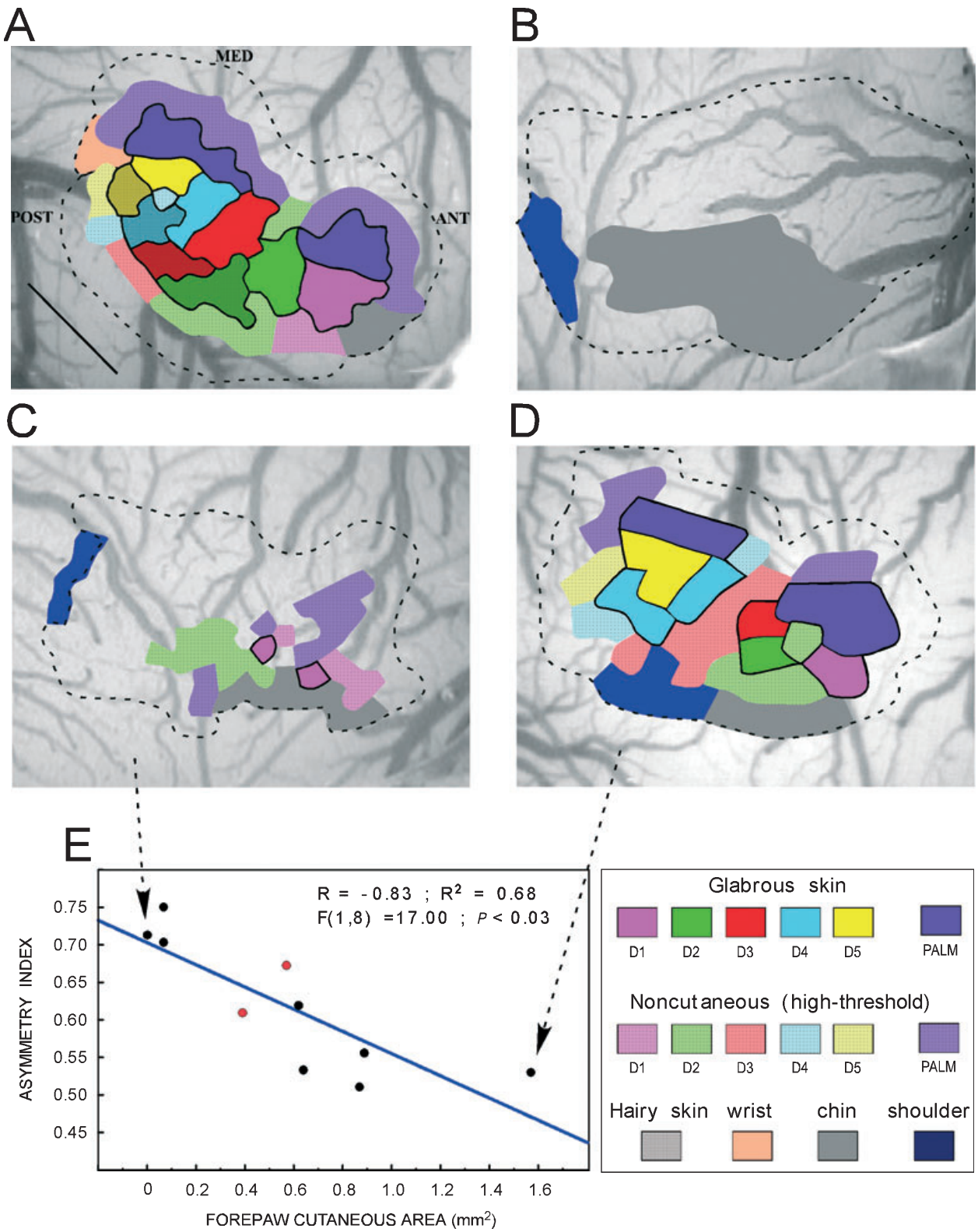


FIG. 5. Changes in the topographic organization of the S1 somatotopic forepaw representation and correlative tactile abilities in LT rats following cervical SCI. Individual cortical maps were obtained from Sh (A), L (B) and LT (C and D) rats. Potentials evoked from somatosensory stimulation were abolished in the forepaw area of the L rats, whereas somatotopically organized cutaneous and non-cutaneous responses were recorded in LT rats at 2 months after the spinal cord contralateral hemisection (B–D). Note the expansion of the chin representation within the adjacent forepaw cortical sectors in the rats (B). The cortical sector mapped with microelectrode recordings is encompassed by dashed lines. Correlation between the post-lesion forepaw perceptual asymmetry score, measured using the adhesive removal test, and extent of recovered cutaneous forepaw representation (E). Note that the smaller the asymmetry, the larger the cutaneous area. Red filled circles refer to the maps obtained as early as the end of the first month post-lesion. D1–D5, digit 1–5. Scale bar: 1 mm. The dashed lines encompass the cortical area mapped with microelectrode recordings. ANT, anterior; MED, medial; POST, posterior.

Examination of cortical maps in LT rats subjected to 7 weeks of sensorimotor training initiated at 1 week after the SCI showed somatotopically organized cutaneous- and non-cutaneous-evoked responses within sectors serving the forepaw (Fig. 5C and D). However, in LT rats, the mean area of these forepaw somatosensory maps was approximately 48% smaller than that of Sh rats ($1.69 \pm 0.54$ vs. $3.54 \pm 0.50$ mm$^2$, respectively; Mann–Whitney $U = 6.0$, $P < 0.003$). In LT rats, cutaneous islets ($0.57 \pm 0.30$ mm$^2$) were found to be embedded into non-cutaneous zones ($1.12 \pm 0.33$ mm$^2$) within the forepaw somatosensory area. The average extent of cutaneous forepaw representation was $30.12 \pm 12.66$% of the entire forepaw somatosensory map. This percentage was significantly smaller than that observed in Sh rats ($63.28 \pm 2.51$%, Chi-squared = 98.18, $P < 0.0001$) in which mean the cutaneous and non-cutaneous areas were $2.25 \pm 0.35$ and $1.30 \pm 0.19$ mm$^2$, respectively.

Interestingly, both cutaneous and non-cutaneous responses were observed after 3 weeks of training in the two LT rats in which electrophysiological mapping was performed at 1 month after the SCI (cutaneous zones: 0.39 and 0.57 mm$^2$; non-cutaneous zones: 0.35 and 1.39 mm$^2$).

### *Relationship between perceptual abilities and forelimb representational area*

Interindividual variability in the recovery of forepaw tactile skills, assessed using the adhesive removal test, led us raise the question as to whether the recovery observed in LT rats might be accompanied by idiosyncratic alterations in individual somatosensory maps. We found that individual AIs were negatively correlated with the extent of the overall cortical area serving cutaneous surfaces in the recovered forepaw representation ($R = -0.83$; $P < 0.03$) (Fig. 5E). The lowest AIs (< 0.60) were found in rats exhibiting forepaw maps in which glabrous skin representations of digit and palm skin surfaces had partially re-emerged. Maps with small islets of glabrous skin surface representations were nonetheless recorded in rats displaying poor tactile abilities. No significant relationship was observed between the animals' tactile performance and the extent of the entire forepaw map including proprioceptive representational cortical sectors ($-0.38$; $P < 0.06$). Therefore, use-dependent recovery of forepaw representational zones appeared to be significantly correlated with improvement in tactile sensitivity.

## Discussion

Our study addressed the question of whether sensorimotor training improved the recovery of sensorimotor performances after cervical spinal hemisection and whether such a rehabilitative effect was accompanied by a remodeling of the impaired forepaw somatosensory map. This SCI resulted in severe unilateral forelimb motor deficits that, in untrained rats, were gradually but partially compensated for over the first post-operative month without further improvement. Indeed, prominent deficits in distal joint control were found to persist to the end of the 2nd month testing period. Although hindlimb deficits were modest and transient, anteroposterior coordination remained impaired even at 2 months post-lesion. In contrast with this spontaneous motor recovery, an enduring loss of forepaw tactile sensitivity was observed. Sensorimotor training resulted in an early, rapid and nearly complete improvement in recovery of motor functions and a more gradual and partial compensation of tactile deficits. Interestingly, this tactile recovery was correlated with a re-emergence, as early as the first post-operative month, of formerly abolished somatosensory-evoked responses in the deprived forepaw area within the S1 cortex.

### *Spontaneous recovery of sensorimotor abilities following the cervical spinal hemisection*

Following a cervical spinal hemisection, ascending and descending pathways are interrupted on one side. During the first 2–3 days following a cervical SCI, the forelimb and hindlimb ipsilateral to the lesion showed flaccid paresis, classically attributed to spinal shock. The substantial spontaneous recovery of locomotor function over the first month followed by continued improvement over the second month and the gradual amelioration of quadrupedal locomotion has been reported (Eidelberg *et al.*, 1986; Webb & Muir, 2002). However, some deficits, notably anteroposterior coupling and forelimb distal impairments, were found to persist. Deficits in paw use following lesion of the main motor tracts involved in the control of distal movements (i.e. rubrospinal and/or corticospinal) have been reported in rats after a hemisection (Anderson *et al.*, 2005; Martinez *et al.*, 2009b) or bilateral lesions of both ventral and dorsal corticospinal tracts at cervical levels (Weidner *et al.*, 2001), and in cats after bilateral lesions of the dorsolateral funiculus at thoracic levels (Jiang & Drew, 1996; for a review, see Drew *et al.*, 2002). The disruption of afferent pathways, which notably results in a persistent loss of tactile function, may be involved in the enduring distal deficits (Schrimsher & Reier, 1993; Bouyer & Rossignol, 2003) as well as in the residual locomotor dysfunction also reported herein (Helgren & Goldberger, 1993; Bouyer & Rossignol, 2003; Webb & Muir, 2003; for a review, see Frigon & Rossignol, 2006). Moreover, hemisection probably impaired intraspinal activity below the lesion site, notably within the neural networks involved in the forelimb and hindlimb coupling during locomotion, thereby resulting in permanent unilateral deficits in anteroposterior coordination (for a review, see Falgairolle *et al.*, 2006). The partial locomotor recovery described in this study could be mediated by increased inputs from the spared contralateral descending pathways, reaching the motoneurons located below the lesion by crossing the midline at the segmental levels or via commissural interneurons (Harris *et al.*, 1994). Furthermore, other mechanisms, such as anatomical rearrangements in axons above and below the injury, may allow descending signals to bypass the lesion (for a review, see Raineteau & Schwab, 2001; Weidner *et al.*, 2001; Bareyre *et al.*, 2004).

### *Imposed sensorimotor training promotes functional recovery after spinal hemisection*

In agreement with previous reports (Eidelberg *et al.*, 1986; Kuhtz-Buschbeck *et al.*, 1996; Fouad *et al.*, 2000; Gulino *et al.*, 2007), we found that sensorimotor training was not critical for a substantial restoration of quadrupedal locomotion after partial SCI but that training-induced locomotion did greatly facilitate the recovery process. In view of the early initiation of locomotor recovery in the trained rats, it is unlikely that collateral sprouting, even if observable a few days after neural injury (Kerschensteiner *et al.*, 2005; Ballermann & Fouad, 2006), is an underlying mechanism, as the time-course of such a structural reorganization would not lead to the emergence of functional changes before the third week post-SCI (Murray & Goldberger, 1974; Fouad *et al.*, 2001; Weidner *et al.*, 2001; Bareyre *et al.*, 2004). Rather, it is well established that use-dependent activity within existing pathways controlling the forelimb and hindlimb musculature is modified through training (for a review, see Edgerton *et al.*, 2001; Barrière *et al.*, 2008), leading to a strengthening of the

neural pathways that sustain activation of locomotion-generating spinal circuitry. Moreover, the repetitive sensory stimulation provided by training has been shown to facilitate the recuperation of rhythmic locomotor patterns (Lovely *et al.*, 1986; Barbeau & Rossignol, 1987; De Leon *et al.*, 1998a; for reviews, see Van de Crommert *et al.*, 1998; Harkema, 2001; Edgerton *et al.*, 2008). Nearly complete motor recovery, including the re-emergence of precise paw placements as observed in our trained rats, could depend on a reinforcement of activity-dependent sensory feedback (De Leon *et al.*, 1998b; Côté & Gossard, 2004) to compensate (at least in part) for the loss of supraspinal inputs to the affected spinal circuits.

### *Training-induced recovery of tactile sensitivity and correlated reactivation of somatosensory maps*

The cervical hemisection led to an enduring deafferentation of the forepaw representational area in the S1 cortex, as demonstrated by the abolition of evoked potentials from forelimb somatosensory stimulation. This finding is consistent with that reported after complete transection of the cervical dorsal columns in adult rats (Onifer *et al.*, 2005). Moreover, the chin representational zone (the afferent input of which was not affected by the lesion) was found to expand into the adjacent forepaw area, in agreement with previous studies (Jain *et al.*, 1995, 1997). Cervical SCI must therefore have interrupted the major pathways for cutaneous and proprioceptive inputs from the forepaw to the contralateral S1 cortex. Nonetheless, anatomical evidence shows that the axons of the spinothalamic neurons, which cross to the contralateral side of the spinal cord and ascend in its ventrolateral quadrant, terminate in thalamic nuclei. Neurons of the spinothalamic tracts are driven by cutaneous and proprioceptive stimuli (Giesler *et al.*, 1979), and thalamic neurons receiving those afferents send diffuse projections to the S1 cortex (Jones & Leavitt, 1974; Tracey, 1995). Our observations suggest that the spinothalamic projections do not mediate suprathreshold responses to cutaneous or proprioceptive stimuli in S1 untrained rats either acutely or chronically after lesion, such that these projections had little effect on layer IV cortical neurons. This finding is consistent with the previously reported extinction of somatosensory-evoked potentials after myelotomy of rat dorsal columns at C4 (Onifer *et al.*, 2005). Furthermore, we observed that cervical hemisection is accompanied by an enduring loss of tactile sensitivity of the ipsilateral forepaw, whereas that of the contralateral forepaw was preserved despite the interruption of its spinothalamic tract. Considered together, our electrophysiological and behavioral findings corroborate the view that the dorsal columns are the principal pathway for both cutaneous and proprioceptive inputs from the forepaw to the contralateral S1 cortex in intact rats.

Our data show that the cortical area serving the deprived forepaw was partially reactivated only in the trained animals, despite the fact that L and LT rats exhibited a similar hemisection and tissue loss, as assessed using MRI completed by histological evaluation. It is unlikely that this reactivation was mediated by fibers running through the lesion site. Previous studies have suggested that reorganization of intraspinal networks sustaining motor functions occurs spontaneously following partial SCI (Fouad *et al.*, 2001; Weidner *et al.*, 2001; Bareyre *et al.*, 2004). Such spontaneous intraspinal reorganization cannot by itself account for the recovery of tactile abilities observed only in our trained rats. Instead, somatosensory inputs from the affected forepaw in these animals must have been conveyed to the contralateral cortex via spinal pathways bypassing the dorsal columns. This substitution may have involved previously latent circuits formed by collateral endings of axons of primary sensory neurons onto spinothalamic neurons. Interestingly, the reactivated forepaw areas were somatotopically organized in these trained rats. This finding may in fact suggest a training-induced synaptic reinforcement or synaptogenesis within pre-existing networks, which thereby allowed the substitutive sensory pathways to maintain the somatotopic distribution of dorsal root fibers entering the spinal cord.

Previous studies have documented a relationship between the extent of cortical representations of cutaneous surfaces engaged in tactile discrimination and corresponding perceptual abilities in both animals (Recanzone *et al.*, 1992; Xerri *et al.*, 1999, 2005) and humans (Pleger *et al.*, 2001, 2003; Hodzic *et al.*, 2004). Without training, our rats displayed a persistent loss of tactile sensitivity associated with an enduring absence of cortical activation in the deprived forepaw representational area (see also Onifer *et al.*, 2005). In contrast, with training, the recovered tactile sensitivity was correlated with the areal extent of restored cutaneous representations serving the forepaw ipsilateral to the hemisection. Taken together, these findings strongly suggest that the re-emergent cortical representations recorded within SI subserved the functional recovery of forepaw tactile abilities.

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## Abbreviations

AI, asymmetry index; L, lesioned; LT, lesioned trained; MRI, magnetic resonance imagery; RF, receptive field; S1, primary somatosensory; SCI, spinal cord injury; Sh, sham-operated.

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