DEFICITS AND RECOVERY OF BODY STABILIZATION DURING ACROBATIC LOCOMOTION AFTER FOCAL LESION TO THE SOMATOSENSORY CORTEX: A KINEMATIC ANALYSIS COMBINED WITH CORTICAL MAPPING

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INTRODUCTION

Numerous studies have investigated functional changes after the induction of large neocortical lesions. By contrast, there are fewer reports of sensorimotor dysfunction after focal neocortical injury. In a previous report, we documented the effects of a restricted unilateral injury to the hand representational zone of area 3b in the primary somatosensory (SI) cortex of monkeys trained on a manual dexterity task (XERRI *et al.*, 1998). We found that this lesion induced transient purely tactile deficits, but enduring sensorimotor impairment. In the early postoperative period, deficits in the precision of ballistic movement, inaccurate hand positioning, disruption of grip formation and inability to execute independent and precisely coordinated finger movements were observed. These sensorimotor deficits subsided and manual dexterity gradually improved over a period of several weeks, until complete recovery was achieved. In addition, we reported correlative changes in the organization of electrophysiological maps in peri-lesion zones of area 3b, as well as in areas 1 and 3a interconnected with the region of the direct damage. This cortical map remodelling was clearly related to rehabilitative effects of training on the dexterity task, presumably through experience-dependent mechanisms of neuroplasticity.

In other studies, we reported evidence that a focal unilateral lesion in the forepaw area of the SI cortex of adult rats induced immediate and longer-term representational reorganization in the spared sectors of the forepaw map (COQ and XERRI, 1999; XERRI and ZENNOU-AZOGUI, 2003). Typically, such focal brain damage induces subtle deficits which are not disclosed when the animals are observed in their daily activities or when conventional tests devoted to assess sensory or motor impairments in rodents are used. In the rat, the SI cortex is topographically organized into a single map representing both cutaneous and proprioceptive inputs. Therefore, we anticipated that an appropriate paradigm using sensitive behavioral measures would allow detection of functional deficits that cannot be evaluated using current methods. To address this question, we used a rotating beam device that we

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had developed in our laboratory to quantify the recovery of acrobatic locomotor balance (XERRI and LACOUR, 1980; XERRI and ZENNOU, 1989). This device was used as a tool for assessing sensorimotor deficits induced by focal injury to the forepaw area of SI, in rats. Moreover, in contrast to most studies in brain-damaged rats, using relatively crude methods and global scales for the assessment of outcome, we performed a 3D motion kinematic analysis for quantifying locomotor impairments and evaluating the time course of recovery. In addition, we combined this quantitative behavioral method with pre- and postlesion electrophysiological cortical mapping to track neurophysiological changes within the spared cortical zones surrounding the lesion. This combination of behavioral and electrophysiological methods was designed to carry out a comprehensive assessment of sensorimotor impairment and to gain insight into the basic neuronal processes of plasticity that may underlie functional recovery after this focal brain injury.

METHODS

Experimental protocol.
This report describes data from 8, 3-month-old adult Long-Evans male rats weighing from 300 to 350 g. Five experimental rats were used for kinematic analysis and electrophysiological mapping. Three rats were used as shams for the kinematic analysis. After weaning (30 days postnatal), littermates were housed in groups of 3 animals for 3 months in Plexiglas cages (26.5 cm wide x 42.5 cm deep x 18 cm high), i.e. in "standard" environmental conditions. The rats were maintained on a 12h:12h light:dark cycle, at constant temperature (23 ± 1 °C) with about 60% relative humidity. Food and water were provided ad libitum. At the age of 3 months, the animals were trained to cross over a rotating beam. The rats' ability to keep their balance during locomotion on the beam was assessed using a kinematic analysis. This test involves balance, coordination and strength of the fore and hindlimbs. After training completion, we recorded neuronal activity in the forepaw area of the primary somatosensory cortex to elaborate a control map. Then, we induced a focal neurovascular lesion targeted to this representational area. Electrophysiological recordings were made during the 2nd hour following the lesion induction to assess initial boundaries of cortical injury. The animals were returned to the animal care facility and were housed singly. The functional deficits and recovery were assessed by resuming the kinematic analysis from the first postoperative day to the end of the 3rd week. The spared regions of the forepaw representation were remapped on the 21st day post lesion.

Kinematic analysis.
The behavioral device consisted of a 2 m long cylindrical beam (diameter: 12 cm) placed 1.2 m from the ground, which was rotated ont its longitudinal axis with a constant linear tangential velocity ranging from 0 to 25 m/min. The rotation could be directed clockwise or counterclockwise with respect to the direction of locomotion. Two compartments at the extremities of the beam allowed the rat to rest between trials and consume a reward consisting of flavored food pellets. A safety net under the beam ensured protection in case of fall. A 15 h food deprivation was used during the preoperative training. No food deprivation was necessary during the postoperative period. The rat was allowed to acclimate to the testing room for 30 min before each training session. For the first training trials, the animal was placed at the center of the beam, facing the goal compartment. For subsequent trials, the rat was placed at the start end of the beam. Initial trials were made on the non rotating beam. After the rats successfully traversed the beam, a rotation was initiated at low velocity. The rotation speed was increased after 4 consecutive trials without a fall. This paradigm was used to grade the difficulty of the locomotor equilibrium task, and hence to test the rat's

ability to produce rapid postural adjustments in order to keep its body balance while compensating for the lateral shift of the continuously moving support. Preoperative training required 6 to 8 morning sessions of about 1h for the rats to stabilize their performance in terms of maximum rotation speed that did not lead to fall. Kinematic analysis was performed with a video motion analyzer (ELITE system, BTS, Milan, Italy). Two infrared video cameras positioned 3.6 m in front of the beam recognized infrared reflecting markers (diameter: 8 mm). Two markers were glued to the skin above the T13 and S4 vertebrae. The ELITE system detects these markers through shape recognition and computes their centroid coordinates for both video cameras. Calibration was performed before each recording session. Marker positions were sampled every 10 ms (100 Hz). The ELITE system elaborated marker trajectories with a 1/3000 accuracy and 3D reconstruction (FERRIGNO and PEDOTTI, 1985). In our experimental conditions, the analysis was restricted to orientation and movements of the rostro-caudal axis of the rat's body. The segment linking the 2 markers was used to measure the orientation and stability of the body axis in the coronal and horizontal planes (Fig. 1). The temporal evolution of the individual markers in the horizontal plane was also recorded as was the lateral angle of the body axis with the beam longitudinal axis.

Surgical preparation.

Experimental procedures were in accordance with the regulations of the NIH guide of Health Guide for the Care and Use of Laboratory Animals (NIH Publications N° 80-23) revised 1996. All efforts were made to minimize the number of animals used and their suffering. Anesthesia was induced with halothane and maintained with sodium pentobarbital (50 mg/kg, i.p.). The animals were kept at an areflexive level of anesthesia throughout the experiment by supplemental administration of diluted pentobarbital (5 mg/kg, i.p.) as needed. The core body temperature was continuously monitored by a rectal thermistor probe and was maintained between 37 °C and 38 °C by a heating pad. The head was held in a stereotactic frame. Surgical and recording procedures were performed under sterile conditions. Posterior neck muscles were resected, and cerebrospinal fluid was drained through an opening in the dura covering the foramen magnum. After a scalp incision and the retraction of attached muscles, a craniotomy (about 16 mm^2) exposed part of the somatosensory cortex (ant.: 2.5 mm; post.: 1.5 mm; lat.: 2-6 mm with respect to bregma). The bone flap was kept in physiological saline at 4 °C. The dura was incised and resected, and the surface of the exposed parietal cortex was bathed in a thin layer of warm silicone fluid (30000 cenistokes; Accumetrics) to prevent drying and oedema. At the end of the recording session, after induction of the cortical lesion, the silicone was removed with a wash of warm saline, the dura was repositioned and covered with a gelatin film (Gelfilm, Upjohn). The bone flap was reinserted and stabilized with dental acrylic. Connective tissue was closed with absorbable sutures and the scalp with silk sutures. The animal's temperature was monitored until the recovery from anesthesia was complete. Prophylactic administration of antibiotic (Pyocefal, Takeda; 150 mg/kg, i.m., in two daily injections) was administered daily for 7 days. On the 21st day after the lesion, the anesthesia procedure was repeated. The bone flap was removed to allow access to the forepaw area of the SI cortex. Then, this cortical zone was mapped. After completion of the remapping procedure, the animal received a lethal dose of sodium pentobarbital (150 mg/kg, i.p.) and the brain was prepared for histological processing. Sham-operated rats were subjected to the same surgical procedure as the experimental animals. This procedure included the dura incision, except that the cortex was left intact. The sham-operated rats were also anesthetized for a similar duration.

Electrophysiological mapping.

A high-resolution camera mounted on an operating microscope was used to digitize images of the exposed parietal cortex, and the ventral and dorsal surfaces of the contralateral forepaw. The recording sites were located relative to the cortical surface vasculature on the digitized image of the cortex and the cutaneous RFs were drawn on the forepaw images, by using Map 0.925 software (PETERSON and MERZENICH, 1995). Neurons were recorded with parylene-coated tungsten microelectrodes (about 1 MΩ at 1 kHz). The electrode was moved perpendicular to the cortical surface in cartesian coordinates using a 3-dimensional micromanipulator driven by stepping motors (Märzhauser). The recording artifact generated by the microelectrode contact with
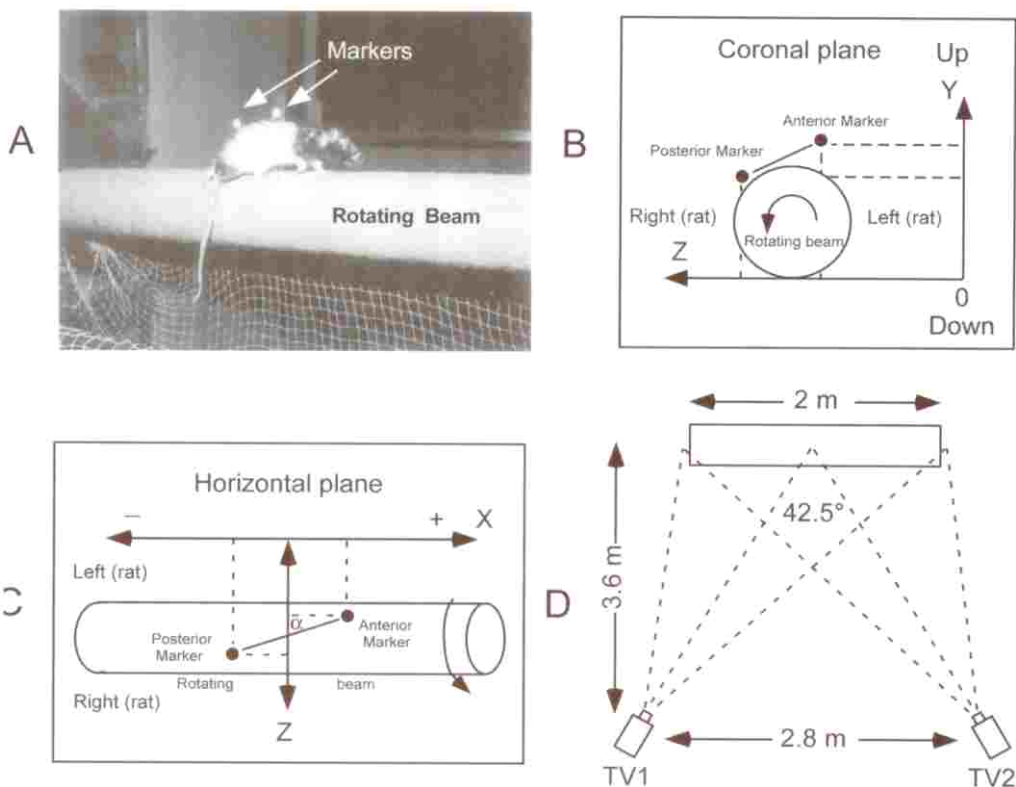
Fig. 1. *Rotating beam device and spatial reference frames used for kinematic analysis.*

A. Motion analysis system (E.L.I.T.E.) allowing computer reconstruction of 3-dimensional trajectories was used to analyze the kinetics of 2 infrared reflecting markers recorded with 2 video cameras. The markers were located along the vertebral axis of the rat to study orientation and coordination of the anterior and posterior parts of the body while the animal was crossing over the rotating beam. **B.** Segment linking the 2 markers recorded in the Y-Z coronal plane (seen from the front) was recorded and reconstructed by computer. **C.** Orientation (α angle) of the segment linking the 2 markers with respect to the longitudinal axis of the beam in the X-Z horizontal plane (seen from above). Independent movements of the markers were also recorded. **D.** Schematic overhead diagram showing the location of the two video cameras (TV1 and TV2) with respect to the rotating beam. As the rat traversed the beam back and forth, beam rotation was toward the intact (left) or affected forelimb (right) after cortical injury.

the cortical surface was used to set a zero level. The electrode was then advanced to a depth of about 650-700 μm to record responses of clusters of 2 to 4 neurons in layer IV. The distance between penetrations averaged 100 μm in all groups of rats. The amplitude of the background noise usually ranged from 15 to 20 μV with a signal-to-noise ratio from 6 to 10. The multi-unit signal was pre-amplified, filtered (bandwidth: 0.5-5 kHz), and displayed on an oscilloscope. This signal was also rectified and passed through a discriminator whose output signal was proportional to the part of the input signal that was higher than an adjustable threshold set just above the background noise. The output of the discriminator was then delivered to an audio monitor. At each recording site, large bursts of activity elicited by natural stimulation allowed us to classify neuronal responses as either cutaneous or noncutaneous, i.e. involving deep receptor, presumably proprioceptive, inputs. Cutaneous RFs were defined as the skin area where just-

visible skin indentation or hair deflection elicited reliable changes in multi-unit activity. This stimulation was produced with a fine-tipped, hand-held glass probe and monitored by using magnifying glasses (x4). In many instances, Von Frey monofilaments (Stoelting, Semmes-Weinstein aesthesiometer) that apply indenting stimuli at a relatively constant, predetermined force were also used. The ridges running along the glabrous skin of the digits and palm were used as landmarks to delineate the RFs. The size of all cutaneous RFs was measured off-line by Map 0.925 software. Noncutaneous responses were identified by more intense stimuli such as taps, pressure on muscles or joint manipulations, when no cutaneous response was found. Cortical sites not exhibiting stimulus-evoked responses but only spontaneous discharges were classified as unresponsive. We used Canvas software (Deneba) to elaborate maps of the forepaw representation by drawing boundaries enclosing the cortical sites in which RFs shared a common skin subdivision, i.e. finger, palmar pad. Boundaries were drawn midway between adjacent recording sites where RFs were restricted to distinct and separate skin subdivisions. A line crossed cortical sites at which a single RF included different but adjoining skin subdivisions of the forepaw. Borders were placed midway between responsive and unresponsive sites. Elaboration of each cortical map was based on a total sample of about 160 to 170 recordings. Canvas software was used to calculate the areal extent of each region of the cutaneous map.

Induction of Cortical Lesion.

The silicone fluid was removed and the exposed cortex was bathed in warm physiological saline. A temperature-monitoring electrode (Radionics TCZ; Kopf; USA) was moved perpendicular to the cortex surface by the micromanipulator and was slowly lowered so that its tip (diameter: 0.25 mm) was in contact with the cortical surface. The lesion was performed at about the center of the forepaw map to spare an amount of tissue that can allow a reorganization of the intact areas surrounding the lesion. A 500 MHz radiofrequency current was delivered through the tip of an electrode equipped with a thermistor. The temperature was gradually raised to 70 °C within 1 min and maintained at this level for 1 min. In addition to destroying neural tissue, the heat generated in the brain tissue induced a focal infarct. This was characterized by a visible occlusion of the vessels, along with a blanching of the cortical zone within the vicinity of the electrode tip. Care was taken to preserve major arteries and veins while occluding their local branches. Radio-frequency induced hyperthermia produces cellular injury, i.e. coagulation necrosis, neuronal shrinkage, nuclear pyknosis and perineuronal astrocytic swelling, (OHMOTO *et al.*, 1996) that is associated with cerebral ischemia. Moreover, localized hyperthermia induces increased extracellular glutamate concentrations that reaches neurotoxic levels (ADACHI *et al.*, 1995).

As in previous studies (JENKINS and MERZENICH, 1987; XERRI *et al.*, 1998) the functional impact of the lesion was assessed using electrophysiological recordings during the 2nd hour postlesion. The boundaries of the cortical infarct were drawn midway between adjacent recording sites which displayed normal response characteristics, i.e. spontaneous discharges and clear responses to peripheral stimulation, and those which exhibited strongly or totally depressed spontaneous activity or stimulus-evoked responses. The surface area of the lesion was measured on the cortex image using Canvas software.

Histological procedure.

Several electrode tracks in each post-lesion experiment were marked with electrolytic lesions at the borders of the forepaw map by passing cathodal current (10 µA DC, 10 s) through the recording electrode. After the mapping session, the rats were given a lethal dose of pentobarbital and perfused transcardially with 0.9% physiological saline followed by a solution containing 4% paraformaldehyde in 0.1% sodium phosphate-buffered (pH: 7.4). The brain was removed and post-fixed in a 4% paraformaldehyde solution containing 10% sucrose in a phosphate buffer. Coronal sections 50 µm thick were cut on a freezing microtome and processed for Nissl staining. Histological sections were used to verify reading locations and to assess cellular changes occurring within the lesioned zone. Extensive loss of cells and gliosis were found from layer I to layer IV, with little or no damage to deep layer V. The injured zone was surrounded by a region of normal architectonic appearance.
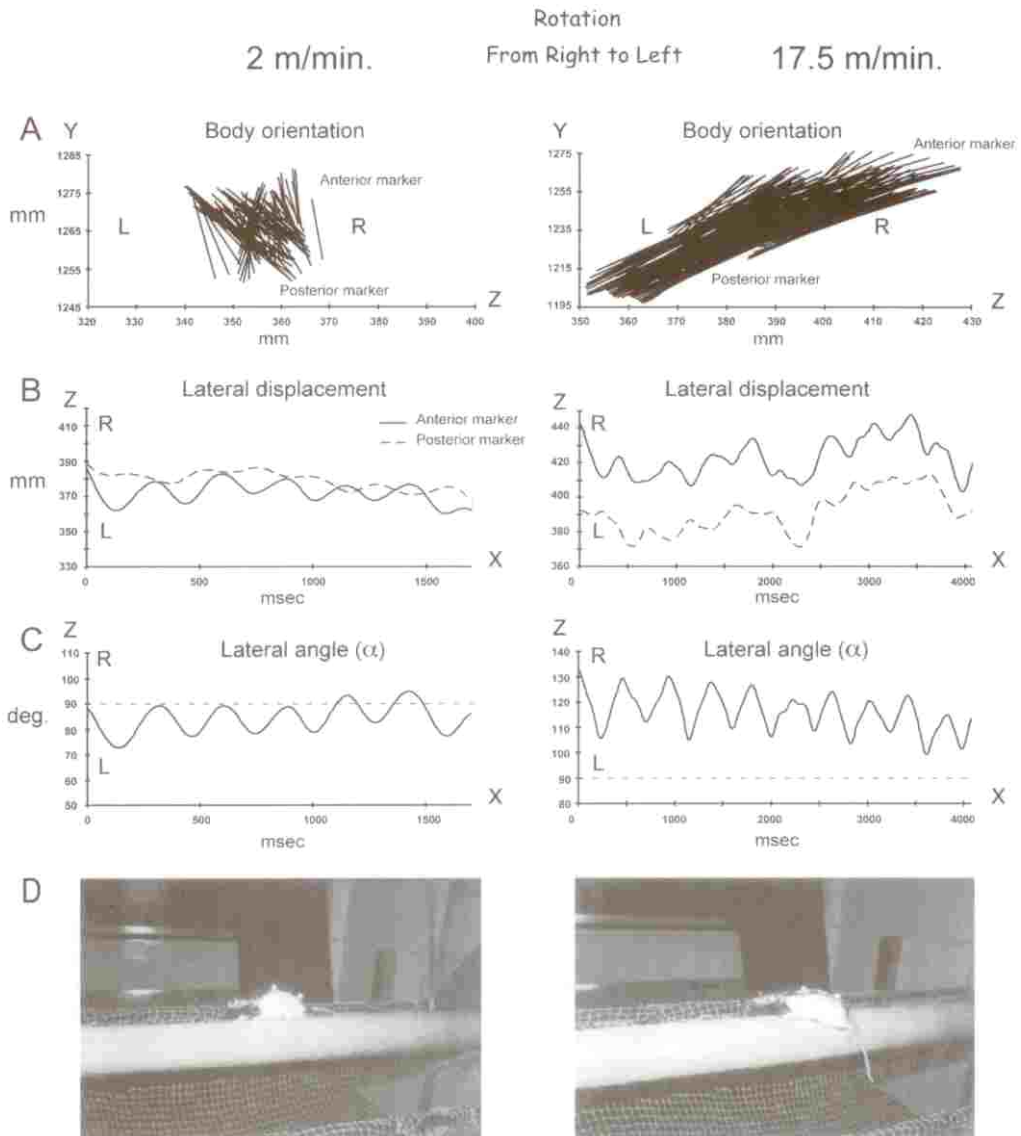
Fig. 2. *Effect of speed of beam rotation on the postural stabilization during acrobatic locomotion.*

A. Segments illustrating the orientation of the body rostro-caudal axis in the coronal plane (vertical corresponds to alignment of the markers along the longitudinal axis of the beam) at low (2 m/min) and high rotation speeds (17.5 m/min). Data was recorded within a 1750 msec (left) or 4000 sec (right) time window during one beam crossing. **B.** Displacement of the markers in the horizontal plane. **C.** Lateral angle (α) formed by the rostro-caudal axes of the rat's body and longitudinal axis of the beam. **D.** Photographs showing the orientation of the body with respect to the beam. Note that the higher the rotation speed, the larger the body deviation in the direction facing the direction of rotation. L and R left and right sides of the rat's body, respectively.

Statistical analysis.

ANOVA was used for statistical treatment of the data. This analysis was supplemented with the Newman-Keuls multiple comparison post-hoc test.

RESULTS

Kinematic analysis.

Figure 2 illustrates typical kinematics recordings obtained for 2 speeds of beam rotation, during the last prelesion training session in one rat. The various orientations and lengths of the coronal plane projections of the segment linking the anterior and posterior markers show that it remained nearly vertical at slow rotation speed (2 m/min) (Fig. 2A). This data indicates that the body rostro-caudal axis was maintained almost parallel to the beam longitudinal axis. By contrast, these segments were tilted and of greater length at a faster speed (17.5 m/min), indicating that the body was deviated with the posterior marker shifting toward the beam rotation direction.

In addition, the kinetic of the markers during beam walking shows that they moved out of phase at a low speed rotation (Fig. 2B). At the same time, we observed that the body waddled smoothly during locomotion on the beam. By contrast, at a faster speed, the markers tended to remain in phase, indicating that the anterior and the posterior parts of the body did not move independently, as the rat displayed a crabwise pattern of walking. At the low rotation speed, the mean lateral angle formed by the rostro-caudal axis of the body and the longitudinal axis of the beam, calculated for the group of 5 experimental rats was -9.8 ± 5.5 deg (450 measurements at a 10 ms sampling period over 4500 ms for each crossing). This value corresponds to a slight lateral deviation of the anterior part of the body toward the direction of beam rotation. The data illustrating the changes of lateral deviation during beam walking shows regular oscillations resulting from body deviations toward the rotation followed by transitory readjustments tending to a realignment of the body rostro-caudal axis with the beam longitudinal axis (Fig. 2C). At the faster rotation speed, the body was deviated toward the opposite direction of the rotation (Fig. 2C-D). The mean value of deviation recorded for the group of 5 rats was 25.7 ± 7.2 deg. As illustrated in Figure 2C, the body axis was no longer realigned with the beam axis, as the rat failed to produce postural adjustments compensating for the lateral shift of the body.

The kinematic analysis showed that unilateral focal cortical ischemia within the forepaw region of the somatosensory cortex induced deficits in gait during locomotion on the rotating beam. Examples of the kinematic data obtained for the 2 m/min rotation are illustrated for different postoperative days in Figure 3. The segments recorded in the coronal plane indicate that the body deviation increased from the 1st day postlesion and tended to return to control values at the end of the 2nd week. Furthermore, the trajectories of the body were not rectilinear, as indicated by the scattering of segments during this postoperative period. In addition, the data illustrating the lateral displacements of the 2 markers shows that the anterior and poste-

rior parts of the body moved in phase, in slow and large waves and with a variable periodicity during the first postoperative days (Fig. 4). The results reveal that the 2 markers tended to again move out of phase from the end of the 2nd week, as recorded prior to the lesion. The lateral deviation of the body, which increased and became
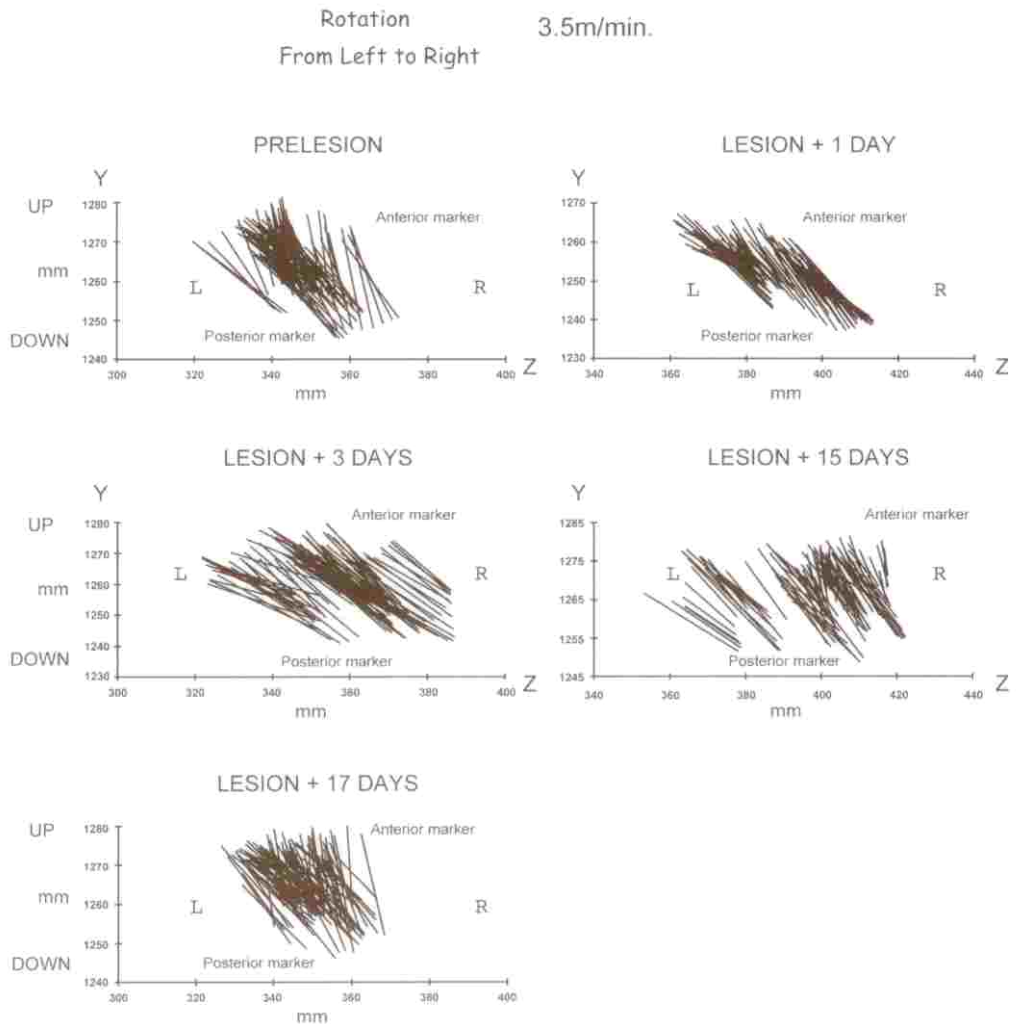

Fig. 3. *Postlesion deficits and recovery of body orientation and locomotion stability recorded in the coronal plane at low speed of beam rotation.*

Example of recordings obtained in an individual rat. Data illustrated here was obtained for rotation toward the lesioned side (right) during a 2000 ms time window. Note that during the first 3 days after the lesion, the deviation of the segments toward the intact side was greater than prior to the lesion. Data also shows a wider scattering of the segments, i.e. a deficit in the ability to maintain a stable orientation of the body during acrobatic locomotion. The body orientation was similar to the preoperative condition from the 15th day postlesion, whereas locomotion stability was recovered from the 17th day postlesion.
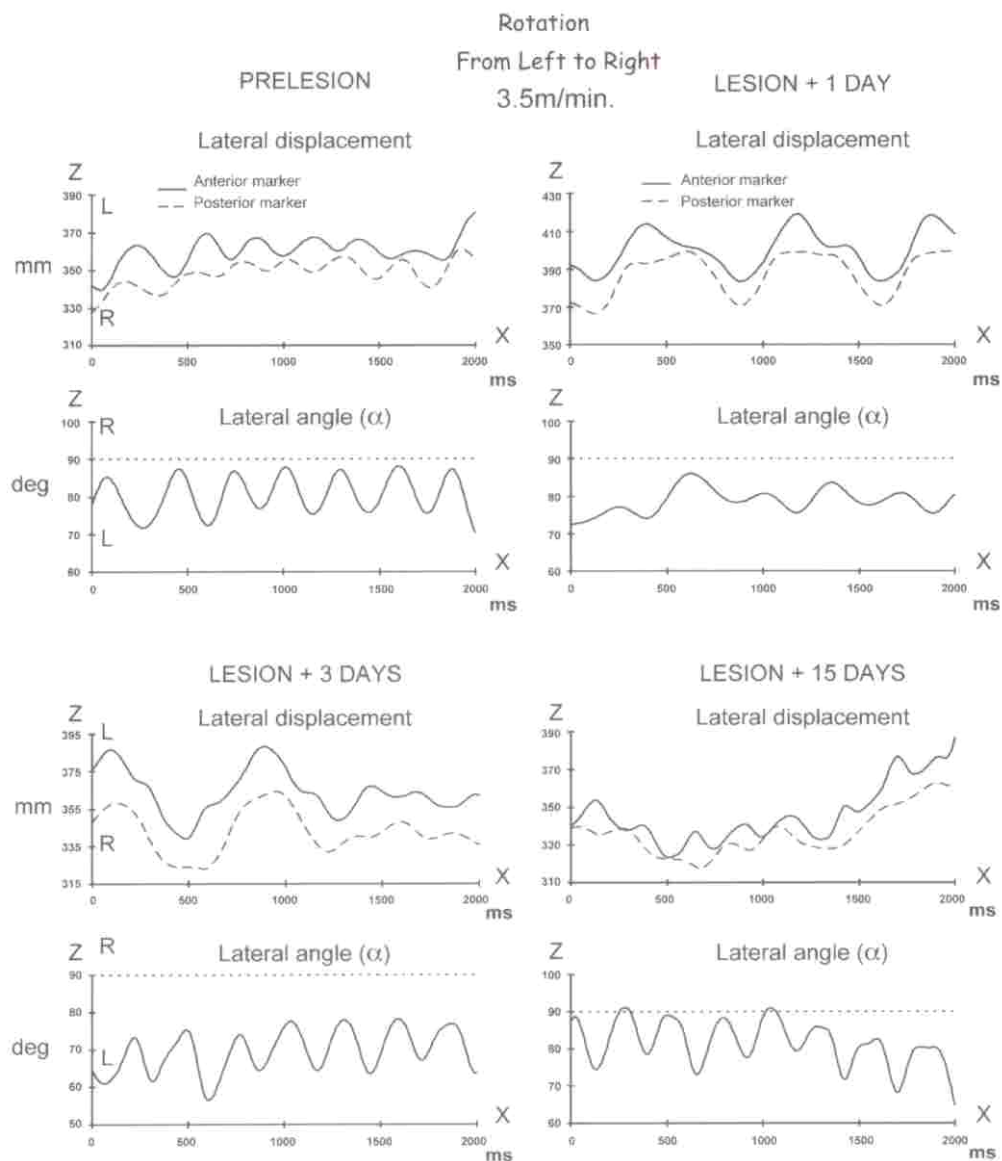
Fig. 4. *Postlesion deficits and recovery of body orientation and locomotion stability recorded in the horizontal plane at low speed of beam rotation.*

Example of recordings obtained in an individual rat. The anterior and posterior markers (upper traces) moved out of phase prior to the lesion, within the low range of speed rotation. These markers moved out of phase in large waves during the first 3 days postlesion. Normal phase opposition and movement periodicity were restored from the 15 day postlesion. The angular deviation of the body (lower traces) became irregular, as the capacity to reorient the body deviated toward the direction of rotation was impaired, only during the first 2 days postlesion. The data corresponds to that illustrated in Fig. 3.

irregular during the first postoperative days was found to be similar to control values on the 17th day. This qualitative observation was confirmed by an ANOVA used to analyze the effect of the lesion on the lateral deviation of the body, in all the animals, for the 12 m/min speed of rotation directed to the right ($F_{32.7} = 9.37$; $P < 0.0003$) of left side of the rat ($F_{32.7} = 8.82$; $P < 0.0005$). This ANOVA completed with the Newman-Keuls test revealed that the lateral deviation of the body was significantly greater than normal during the 1st postoperative week and returned to control values from the 9th day postlesion (Fig. 5). The data obtained in the sham-operated rats indicates that the surgical procedures and anaesthesia did not result in locomotor dysfunction. The mean deviations calculated on the 1st and 3rd day postlesion for all rats was greater for rotations toward the impaired forelimb (14.12 ± 4.43 deg. and 21.8 ± 4.72 deg.) than the intact forelimb (8.61 ± 2.05 deg. and 13.9 ± 3.28 deg.) both at 12 m/min ($F_{28.1} = 13.10$; $P < 0.003$) and 17 m/min ($F_{28.1} = 18.09$; $P < 0.0004$), respectively. These results suggest an asymmetrical effect of the forelimb impairment during locomotion on the beam at relatively high speeds of rotation. A nearly complete recovery of normal body deviation was found about 10 days after the lesion (Fig. 5).

Cortical mapping.

In previous reports, we have described the somatotopic organization of the forepaw representation within the SI cortex of Long-Evans rats (COQ and XERRI, 1998). Examination of the forepaw map points out invariant organizational features despite interindividual differences. Briefly, the forepaw map is somatotopically organized in the rostrolateral-caudomedial direction, from the thenar eminence and digit 1 to the hypothenar eminence and digit 5, and in the rostromedial-caudolateral direction, from the palmar pads to the glabrous and hairy skin surfaces of digits (Fig. 6A). The palm representation is situated along the medial edge of the map in two distinct cortical sectors serving: 1) the thenar eminence and the first pad, in the vicinity of digits 1 and 2 representations, and 2) the second and third pads, and the hypothenar eminence in the region adjoining digits 4 and 5 representations. The representation of the hairy skin of the digits is located laterally to that of the glabrous skin of the corresponding digits. The external boundaries of the forepaw cutaneous map are consistently delimited by noncutaneous responses. The cortical regions representing contiguous skin surfaces are usually interspersed with noncutaneous islets. The average area of the forepaw maps calculated in the intact rats was 2.27 ± 0.29 mm².

The focal neurovascular lesion was centered on the cortical zone serving the ventral skin surfaces. The area of the injured cortical zone, assessed with electrophysiological recordings during the 2nd hour postlesion was 0.71 ± 0.25 mm², which corresponded to an average of 31.30 ± 8.20% of the whole cutaneous area of the forepaw representation, defined as the area including glabrous and hairy skin representational sectors of the map (Fig. 6B). We calculated the spared area of the "acute" cutaneous map (1.57 ± 0.32 mm²) by subtracting the area of the lesion from the area of the intact cutaneous map. Then, we compared this acute area with the spared cutaneous area recorded 3 weeks after the lesion induction, referred to as "chronic" (0.95 ± 0.36
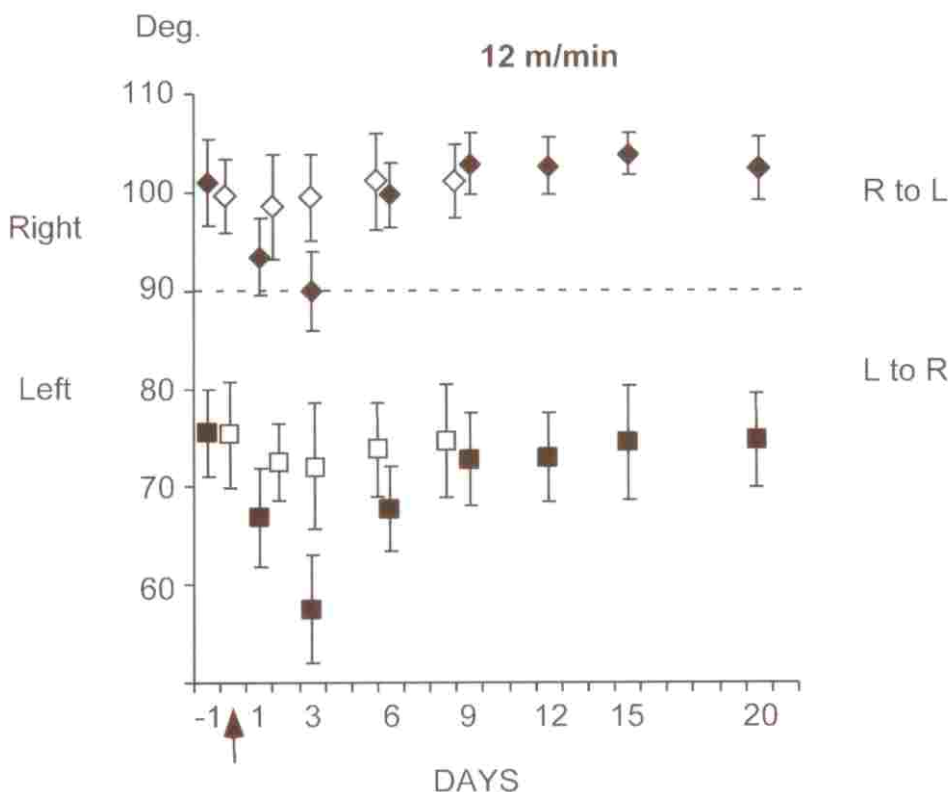
Fig. 5. *Postlesion deficits and recovery of lateral body deviation.*

Mean (± S.D.) lateral angle calculated for the experimental (filled symbols) and sham-operated rats (open symbols) at the 12 m/min rotation speed, prior to the lesion and during the first 3 postoperative weeks. Note a transient increase of the lateral deviation from the 1st to the 9th day postlesion (90 degrees corresponds to a perfect alignment of the rat's and beam axes). This deviation was greater for rotations to the lesioned side (right). The arrow indicates the day of lesion induction.

mm^2). The relative change in the spared area over the weeks following the injury was calculated as follows: [(chronic area - acute area)/acute area] X 100. The results show a further representational loss of -39.50 ± 9.40%, i.e. a total loss of about 60% of the intact forepaw area (Fig. 6C). However, reemergence of some skin surface representations was noted in the peri-lesion zone. Interestingly, the loss of representation recorded in the present study was smaller than that obtained in a previous investigation (-63.19 ± 10.31%; $F_{8,1}$ = 38.05, P < 0.001) in which the rats underwent a similar lesion (29.36 ± 5.89%), were also housed singly, but were not subjected to behavioral training (XERRI and ZENNOU-AZOGUI, 2003). Consequently, the spared cortical areas recorded in the trained rats (0.95 ± 0.36 mm^2) were, on average, greater than those found in the untrained rats (0.52 ± 0.30 mm^2). It is also relevant to mention that the prelesion maps (2.27 ± 0.29 mm^2) obtained from our trained rats housed in groups of

3 before the surgery were not significantly larger ($F_{8,1} = 8.1$, P: n.s.) than those of untrained rats housed in the same conditions (2.14 ± 0.37 mm^2) (data from COQ and XERRI, 1998).

The areas of the glabrous or hairy skin RFs were measured in mm^2, expressed as a percentage of corresponding ventral or dorsal skin areas of the forepaw and then averaged for each rat. Acute postlesion RFs were obtained by removing the RFs corresponding to the cortical sites located within the boundaries of the injury from the prelesion populations of RFs (Fig. 6B). The sizes of acute postlesion RFs (glabrous: $7.20 \pm 1.6\%$; hairy: $9.14 \pm 2.43\%$) were compared to that of chronic postlesion RFs (glabrous: $7.69 \pm 2.1\%$; hairy: $8.84 \pm 3.20\%$). The ANOVA yielded no significant differences between these RF populations either for the glabrous ($F_{8,1} = 2.3$, P: n.s.) or hairy skin surfaces ($F_{8,1} = 1.9$, P: n.s.) (Fig. 6B-C).

DISCUSSION

Deficits in fine sensorimotor adjustments during acrobatic locomotion.

The present study documents impairments of motor adjustments during acrobatic locomotion on a rotating beam after a focal injury to the forepaw area of the SI cortex. Our purpose was not to provide a precise and inevitably complex reconstruction of the kinetics of forelimb and hindlimb movements. The kinematic analysis was restricted to 2 markers as an attempt to describe in a relatively simple manner the lesion-induced alterations in the movements and coordination of the anterior and posterior parts, and the orientation of the rats' body. Our findings show that a small, but rapidly expanding lesion (COQ and XERRI, 1999) initially restricted to about 30% of the forepaw representational zone was sufficient to give rise to conspicuous impairments in the rats' ability to produce adequate motor adjustments compensating for the lateral shift of the beam and stabilizing the posture on this constantly moving support. The main deficits were reflected in a lack of appropriate coordination and synergy between the anterior and posterior parts of the body. This resulted in a difficulty to adopt a normal body orientation, attested by a crabwise walking pattern, and an inability to maintain a regular gait during locomotion, indicated by erratic movements of the body as the animals traversed the beam. These deficits occurred even at low speed beam rotations, although the need for a fine control of locomotion was not as important as for high speed rotations. These functional deficiencies can partly be ascribed to impairments in the capacity to utilize sensory information from the forepaw to produce rapid postural adjustments required to ensure proper regulation of acrobatic locomotion.

Indeed, somatosensory inputs play a crucial role in the regulation of all motor activities, including postural control. Indeed, besides other sensory systems (vestibular and visual) the somatosensory system contributes to preserve balance and ensure stability of the body during locomotion (ZEHR and STEIN, 1999 for review). The sensory information arising from skin, muscles and joints is integrated into internal commands in the driving of motoneurons, or can be used as an error signal to correct the execution of an ongoing movement. During locomotion, particu-
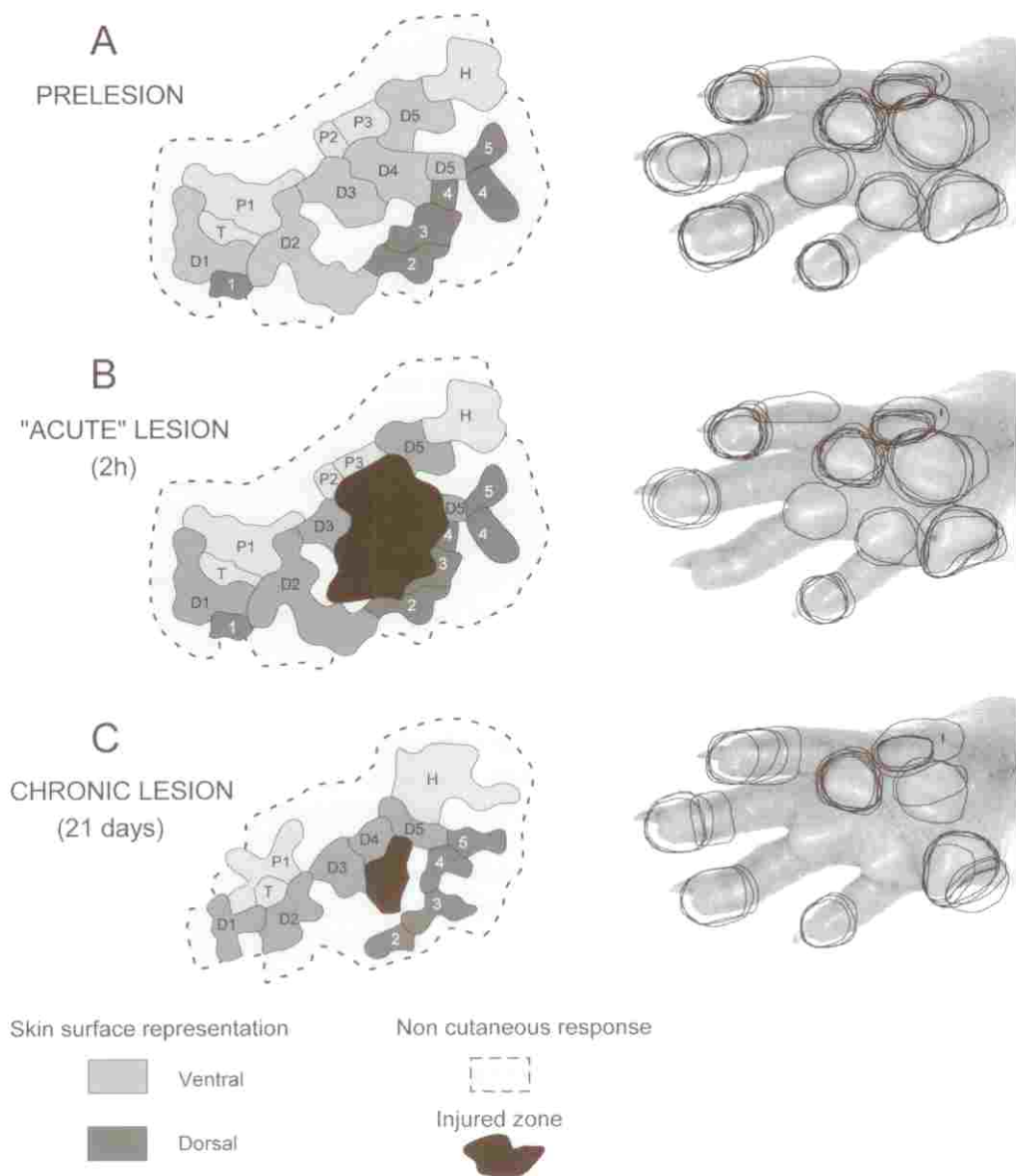
A

PRELESION

B

"ACUTE" LESION
(2h)

C

CHRONIC LESION
(21 days)

Skin surface representation

Ventral

Dorsal

Non cutaneous response

Injured zone

Fig. 6. *Remodeling of the somatotopic maps of the forepaw after focal cortical lesion.*

Left: Double electrophysiological mapping illustrating the forepaw representations recorded prior to (**A**) and 3 weeks (**C**) after the lesion induction in the same rat. The injured, electrophysiologically silent, area defined on the basis of neuronal recordings performed during the 2nd hour 1h after the lesion induction is shown on the prelesion map (**B**). Note that the injured area was smaller in the map elaborated 3 weeks after the lesion induction, due to substantial cellular loss. D1-D5: digit 1 – digit 5 ventral skin areas; 1-5: digit 1 – digit 5 dorsal skin areas; P1-P3: Pad 1 – Pad 3; T: thenar eminence; HT: hypothenar eminence.
Right: Cortical neurons' glabrous skin receptive fields used to elaborate the cortical maps shown on the left.

larly in case of external perturbation, it is likely that cutaneous and muscle reflexes act in concert in an integrative manner to finely regulate and restore postural orientation and body balance. FORSSBERG (1979) was the first to provide evidence of the functional role of cutaneous reflexes in a "stumbling corrective response" allowing to clear obstacles and to maintain stability of quadrupedal locomotion (WAND, 1980; McCREA, 1998). In a study combining electromyographic (EMG) and kinematic techniques, DREW and ROSSIGNOL (1987) reported cutaneous reflexes in the cat forelimb suggesting an important role of cutaneous inputs in correcting limb movement during locomotion. Furthermore, cutaneous reflexes from the skin of the foot have been shown to contain location-specific information leading to distinct reflex responses and synergies during walking (VAN WEZEL et al., 1997). The sensorimotor deficits reported in the present study give, to some extent, insight into the contribution of sensory information arising from or transiting through the primary somatosensory cortex. This contribution is of primary importance during the execution of a task requiring fine locomotor adjustments to compensate for external perturbations and to avoid falling. It is worth mentioning that dorsal rhizotomy can eliminate premovement-related SI activity (BIOULAC and LAMARRE, 1979). Also of interest to the present study is the finding that unilateral SI cooling causes deficits in the motor control of the distal contralateral forelimb (BRINKMAN et al., 1985). A relatively recent series of studies has clarified the fact that transcortical reflex pathways from cutaneous afferents involving the somatosensory cortex and corticospinal tracts can mediate the regulation of posture. This points out that activation of cutaneous afferents from the foot can modulate through long-latency facilitation the motor cortex output evoked by transcranial magnetic stimulation (NIELSEN et al., 1997). Moreover, it has been shown in the monkey that cutaneous afferents from the limbs modulate the discharge of neurons in the motor cortex (TANJI and WISE, 1981). In addition, there is evidence that anatomical integrity of the dorsal columns, the somatosensory cortex and the corticospinal tract is required to generate a late reflex in the EMG of foot muscles following cutaneous stimulation (JENNER and STEPHENS, 1982; ROWLANDSON and STEPHENS, 1985). The functionally relevant implication of transcortical reflex mechanisms following perturbations in stance (MARPLE-HORVAT et al., 1993) and during precision walking (MARPLE-HORVAT and ARMSTRONG, 1999) has been underscored. Interestingly, corticospinal neurons originating in the granular somatosensory cortex terminate in the medial portion of the dorsal horn in rats (LI et al., 1985). Therefore, these projections may modulate motor responses. Based on the findings reported above, one can hypothesize that in the present study, focal injury to the forepaw area of the SI cortex may have disturbed the transcortical reflexes that subserve a postural regulative function, through disruption of the central integration of afferent input from the forepaw, thereby accounting for the dysfunctional locomotion.

Functional recovery.
Our kinematic data shows that deficits in the rat's ability to properly compensate for the lateral shift of the beam were gradually attenuated and that skilled locomo-

tion was fully recovered within a 2-3 week period. The functional recovery cannot be ascribed to a full restitution of the lost sensory representations since a permanent decrease of forepaw representation was recorded. It has long been documented that sensorimotor experience before and after brain injury can enhance functional outcome. For example, exposure to enriched environments after damage to various brain areas ameliorates behavioral recovery in rodents (WHISHAW *et al.*, 1984; HELD *et al.*, 1985; GALANI *et al.*, 1997; RISEDAL *et al.*, 2002). It is also of interest that 2 weeks after a middle cerebral artery occlusion, environmental enrichment combined with daily training on a motor skill task improves functional restoration of skilled use of the impaired forelimb (BIERNASKIE and CORBETT, 2001). Rats with small lesions to the sensorimotor cortex which experienced complex motor skill tasks, displayed improved coordination of the forelimbs, compared with rats receiving simple locomotor exercise (JONES *et al.*, 2003) Along the same line, rats having extensive locomotor experience following cortical lesions displayed reduced deficits and faster recovery in a behavioral test consisting in walking on a narrow, immobile beam (HELD *et al.*, 1985). Rehabilitative motor skill training has also been shown to improve recovery of hand motor skill after focal lesions to the motor (NUDO *et al.*, 1996) or somatosensory cortices (XERRI *et al.*, 1998). In the latter study, evidence was given that the manual skill recovery resulted from a relearning process. In our experimental conditions, as the locomotor task was resumed early after the injury, one can assume that repeated sensory feedback signals over successive trials were used to readjust the motor commands and were eventually integrated into the built-in motor programmes, as a substrate for sensorimotor relearning and recovery of skilled locomotion. These corrective signals may originate from somatosensory, vestibular or visual receptors. Conceivably, the functional recovery may involve an increased reliance on all theses sources of sensorimotor regulation. Direct connections between visual, somatosensory and motor cortices have been evidenced in the rat (MILLER *et al.*, 1984). These corticocortical pathways provide the basis for multisensory integration that may aid the rat in the coordination of visually and somatosensory guided behaviors. This multisensory integration may be useful to optimize adaptation to the damage and/or mediate compensation for the locomotor deficits through a substitution process, after injury to the SI cortex. In addition, one cannot exclude the developpement of compensatory movement patterns or the recourse to alternative behavioral strategies to circumvent functional deficits, like an increased use of intact forelimbs to ensure postural stabilization while traversing the rotating beam. Indeed, an enhanced use of the nonimpaired forelimb in a footfault task has been reported after unilateral damage to the forelimb sensorimotor cortex in rats (SCHALLERT *et al.*, 1997). Local anesthetization of the nonimpaired forelimb produced a reinstatement of the impaired forelimb deficits. The improvement in performances that involved the intact forelimb was enhanced in rats trained on an acrobatic task which required the animals to learn complex movement coordination to traverse a series of obstacles (JONES *et al.*, 1999).

It is plausible that early retraining limited the expansion of the cortical injury, and thus tended to partially preserve the forepaw representation in the peri-injury zone,

thereby contributing to a faster recovery. Indeed, in a previous electrophysiological mapping study, we reported that small neurovascular lesion to the SI cortex exhibited a significant expansion developing from the first hours postlesion and leading to neuronal damage. This expansion resulted in an additional 50 to 60% loss in cutaneous representations 12h after the lesion induction (COQ and XERRI, 1999). In a recent paper, we have showed that the remaining cortical zone devoted to the forepaw representation had further decreased 3 weeks after the lesion induction, as a result of this growing injury (XERRI and ZENNOU-AZOGUI, 2003). In this latter study, rats were subjected to cortical damage very similar to that performed in the present one. They were also housed singly after the lesion, but received no behavioral training. In the present study, rats trained to acrobatic locomotion, exhibited prelesion forepaw maps of similar extent compared to those of untrained rats, but exhibited spared forepaw areas significantly larger than that recorded in untrained rats. This finding suggests that the sensorimotor experience inherent to the locomotor task tended to preserve, at least partially, the representational sectors within the cortical region surrounding the site of initial injury. In a study cited above (XERRI et al., 1998), in which monkeys were trained on a digital dexterity task before and after a focal ischemic lesion to area 3b of SI, the extent of cortical damage measured after full recovery was very close to the extent of the lesion estimated at the time of its induction. Thus, this finding revealed that postlesion retraining can exhibit a neuroprotective effect. In addition, we found that this retraining induced substitutive representational changes in areas 3b, 3a and 1, thus revealing a striking degree of distributed representational remodeling after focal cortical lesions. These changes were specifically related to the skin surfaces preferentially engaged in the manual dexterity task. In the rat's neocortex, SI is comprised of a single somatotopic area. Therefore, injury to SI limits the capacity for adaptive representational remodeling within the same area. Direct input from the ventrobasal complex of the thalamus to the second area of somatosensory cortex (SII) (WELKER and SINHA, 1972) and the motor cortex (WISE and JONES, 1978), as well as intracortical ipsilateral connections between SI, SII and motor cortices (AKERS and KILLACKEY, 1978) might be involved in a compensatory process and underlie representational reorganization in ipsilateral areas remote from the injury site. In addition, one cannot exclude the possibility that representational changes take place in the contralateral intact hemisphere. Indeed, increased cutaneous RFs have been recorded in the hindpaw homotypic area opposite the hemisphere affected by a focal cortical infarct to the hindpaw area of SI, in rats (REINECKE et al., 2003). This RF enlargement presumably resulted from GABAergic disinhibition induced by the cortical injury (BUCHKREMER-RATZMANN et al., 1996; REINECKE et al., 1999), which was associated with a down-regulation of GABA$_A$ receptor binding and subunits (NEUMANN-HAEFELIN et al., 1999). Also of relevance to the present study is the finding that, after unilateral damage to the forelimb area of the rat sensorimotor cortex, compensatory reliance on the nonimpaired forelimb for postural support behaviors is associated with morphological alterations in layer V pyramidal neurons of the homotypic intact forelimb area. These alterations include increased dendritic arborization (JONES and SCHALLERT, 1992), den-

dritic spine density (KOZLOWSKY *et al.*, 1994) and synapse to neurons ratios (JONES *et al.*, 1996). These dendritic modifications were not found when movements of the nonimpaired forelimb were restricted (JONES and SCHALLERT, 1994). Moreover, postoperative learning of motor skills that required complex sensorimotor coordination, enhanced synaptogenic responses in layer V of the opposite motor cortex (JONES *et al.*, 1999). It is conceivable that the biochemical, morphological and neurophysiological changes that take place in remote areas functionally interconnected with the damaged cortical zone play a substantial role in functional recovery. However, a recent study suggested that the degree of reorganization in the forelimb regions of the somatosensory and motor cortices contralateral to the lesion increases with the extent of injury and that the functional restoration is associated mainly with preservation or restoration of activation in the injured hemisphere (DIJKHUIZEN *et al.*, 2003).

SUMMARY

We used a kinematic analysis for assessing locomotor impairments and evaluating the time course of recovery after focal injury to the forepaw area of the primary somatosensory cortex (SI) in rats. The animals were trained to traverse a beam that was rotated at various speeds. Changes in orientation of the body and independent movement of the anterior and posterior parts of the body were reconstructed using a 3D motion analysis. In addition, we used electrophysiological cortical mapping to search for neurophysiological changes within the spared cortical zones surrounding the lesion. Neuronal recordings were performed in the same animals prior to and 3 weeks after the lesion induction. Our findings show that a focal lesion that destroyed about 60% of the forepaw representational zone was sufficient to cause conspicuous impairments in the rats' ability to produce adequate motor adjustments to compensate for the lateral shift of the beam and to avoid falling. The main deficits were reflected in a lack of appropriate coordination between the anterior and posterior parts of the body and an inability to maintain a regular gait during locomotion. Skilled locomotion was fully recovered within a 2-3 week period. Functional recovery cannot be ascribed to a restitution of the lost sensory representations. A permanent decrease of forepaw representation was recorded despite the re-emergence of restricted representational sectors in the peri-lesion zone. We suggest that alterations may have occurred in other cortical and subcortical areas interconnected with the injured area. It is also conceivable that the functional recovery involved an increased reliance on all the available sources of sensorimotor regulation as well as the use of behavioral strategies.

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