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# Effects of a Rostral Motor Cortex Lesion on Primary Motor Cortex Hand Representation Topography in Primates

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## Abstract

**Background—**Small lesions to rostral versus caudal portions of the hand representation in the primary motor cortex (M1) produce different behavioral deficits. The goal of the present study was to determine if rehabilitative training has similar effects on functional topography of the spared M1 after rostral versus previously reported caudal M1 lesions.

**Methods—**Following a lesion to the rostral M1 hand area, monkeys were trained for 1 h/day for 30 days to retrieve food pellets from small wells using their impaired hand. Electrophysiological maps of the M1 were derived in anesthetized monkeys before infarct and after rehabilitative training using intracortical microstimulation.

**Results—**After a lesion to the rostral M1 and rehabilitative training, the size of the spared hand representation decreased 1.2%. This change is not statistically different from the 9% increase seen after caudal M1 lesion and rehabilitative training ($P > 0.2$).

**Conclusion—**Postlesion training spares peri-infarct hand area regardless of whether the lesion is in the rostral or caudal M1.

### Keywords

Recovery; Rehabilitation; Cortical plasticity; Stroke

It is now well established that cortical physiology changes over the lifetime of an animal, modulated by learning, central nervous system injury, or peripheral nervous system injury (reviews1–5). Learning-and injury-dependent cortical plasticity have been studied extensively in the somatosensory and motor cortex.

In the somatosensory cortex of animals, skin surfaces of the digits and hand are represented topographically. The normal, highly organized topographic arrangement of the digit skin surfaces can be modulated by learning or by injury. When monkeys were trained on a tactile discrimination task using 1 digit, the representation of the trained digit increased in size in the cortex.6–8 Additionally, if the skin surfaces of adjacent digits are surgically fused, the cortical representations of the fused digits become intermixed.9,10 After a digit is surgically amputated, representational areas of adjacent digits invade the cortical territory that once contained the representational area corresponding to the amputated digit.11

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Similar learning- and injury-dependent changes have been documented in the motor cortex in animal models. Training on a pellet-retrieval task caused an expansion of the digit representational area in the motor cortex in rats12 and nonhuman primates.13 Training on a key-turning task resulted in an expansion of wrist and forearm representational areas in nonhuman primates.13

Motor cortex lesions produced changes in cortical physiology that were dependent upon the postlesion experience of the animal. After primary motor cortex (M1) lesions, if monkeys did not receive any rehabilitative intervention, the size of the hand representation surrounding the lesion decreased dramatically.14 However, when animals received rehabilitative training using the impaired arm, the prelesion size of the hand representation surrounding the lesion was maintained after the lesion.15–17

Motor cortex lesions not only alter cortical physiology but also cause motor skill deficits.2, 17–29 For example, in adult rats, motor cortex lesions produce deficits in manual retrieval of food rewards.29 Likewise, motor cortex lesions in nonhuman primates produce deficits in skilled hand use. Monkeys exhibit a decreased ability to retrieve objects,18,27,28,30,31 track a target with the wrist,25 and grip an object with the hand.22

Considerable evidence suggests a parcellation of the primate M1 into rostral (M1r) and caudal (M1c) components. This evidence is based on neurophysiological, neuroanatomical, neurochemical, and hodological differences.32–35 The M1 receives sensory inputs from somatosensory cortical areas and from the thalamus. These inputs are believed to be important in the regulation of sensory-related aspects of motor control. Sensory inputs to the motor cortex are segregated within the M1; the M1r receives a predominance of proprioceptive information, whereas the M1c receives proprioceptive as well as cutaneous information. More recently, it has been demonstrated that cortico-cortical connectivity differs substantially between the M1r and M1c (more specifically, rostrolateral M1 vs. caudomedial M1).36

A recent study in squirrel monkeys compared the effects of M1r and M1c lesions on skill in retrieving food pellets from small wells.37 After a caudal M1 lesion, monkeys frequently examined their palm visually for the presence of a food pellet after an attempted retrieval, possibly indicative of a cutaneous sensory deficit similar to a somatosensory agnosia. After a rostral M1 lesion, monkeys frequently failed to accurately direct the hand to the well. Instead, fingers touched the surface of the board outside of the well before entering the well. These errors in aiming may indicate a proprioceptive deficit. Similar location-specific deficits were seen after local inactivation of the M1 in cats.38,39

Because there are several structural and functional differences between the M1r and M1c, we examined differences in cortical maps after M1r versus M1c lesions. Cortical map changes following lesions to the caudal portion of the M1 hand area have been documented previously in detail.14,15,40 One month after a lesion to the caudal portion of the M1 hand representation, the size of the hand representation surrounding the lesion decreased substantially14 unless animals received daily rehabilitative training using the impaired hand in a skilled way.15 Unskilled use of the impaired hand was not sufficient to retain the hand representation surrounding the lesion.18

The present study compared cortical maps of the M1 hand representation before and approximately 1 month after a lesion to the rostral portion of the M1 hand representation. The goal of the study was to determine if skilled rehabilitative training produced adaptive changes in cortical physiology after M1r lesions, similar to the established adaptive changes observed after M1c lesions and rehabilitative training. Rehabilitative training of the affected side in stroke patients has shown promise in promoting long-term recovery of motor skills.41–44 It

is important to determine whether skilled rehabilitative training can be useful therapeutically despite different locations of lesions within the M1.

Changes in cortical topography after rostral M1 lesions were then compared to previously published results describing changes in cortical topography after caudal M1 lesions.14,15,40 This study demonstrates that behavioral training leads to retention of spared M1 hand representational area after either M1r or M1c lesions, emphasizing the importance of postinjury rehabilitative training of the affected limb in maximizing the neurophysiological integrity of the damaged system.

## MATERIALS AND METHODS

Four adult squirrel monkeys (genus *Saimiri*), 2 males and 2 females, were used in the present study. Animals ranged in age from approximately 2 to 9 years and weighed 700 to 900 g. The general procedures were conducted as follows: 1) hand preference testing, 2) preinfarct motor training, 3) neurophysiologic mapping and cortical lesion, 4) postinfarct behavioral (rehabilitative) training, and 5) neurophysiologic mapping after postrehabilitative training. Each of these procedures is described in detail below, in chronological order. These procedures are identical to those used previously in this laboratory to examine neurophysiological changes after M1c lesions. Behavioral results from these animals are published.37 All procedures were approved by the University of Kansas Medical Center's Institutional Animal Care and Use Committee.

### Behavioral Methods

**Hand preference testing—**The hand preference of each animal was determined by testing on a modified Klüver board, a 24 × 7.6 × 1.8 cm rectangular Plexiglas apparatus containing 5 cylindrical wells evenly spaced on the top surface of the board. The diameters of the wells were 25, 19.5, 13, 11.5, and 9.5 mm. Each well was 5 mm deep and had a conical bottom. The Klüver board was attached to the front of the monkey's cage, and the monkey reached between the cage bars to retrieve pellets from the food wells (Fig. 1). Hand preference testing consisted of 50 trials per day for 2 consecutive days. Each trial began when a 45 mg food pellet (Bio-Serv, Frenchtown, NJ) was introduced randomly into 1 of the 5 wells. Each trial ended when the monkey retrieved the pellet and brought it inside the cage. All trials were recorded using a video camera (Sony, New York, NY). The orientation of the board was counterbalanced between the 2 days to reduce the possibility of position bias.

To determine hand preference, videotapes of trials were reviewed using a Hi-8 videocassette editing deck (Sony). The hand used in each reach was tallied, and the hand used in over 50% of successful retrievals was designated the dominant hand. It was necessary to determine each animal's hand preference at the beginning of the experiment because for the remainder of the experiment, each monkey's nondominant arm would be restrained by a mesh sleeve.

**Prelesion training procedure—**After hand preference was determined, each animal was fitted with a mesh jacket that had a mesh sleeve enclosing the nondominant arm (Fig. 1). The sleeve was closed at the distal end, disabling the animal from using its nondominant hand to retrieve pellets from the Klüver board. The animal was able to use its sleeved arm for climbing and balance.

After the monkey was fitted with the jacket, prelesion training began. Each session consisted of 25 probe trials followed by 30 min of training. Prelesion training was required to familiarize the animals with the task, so that postlesion deficits could be attributed to lesion-induced skill loss rather than training or learning effects. Two training sessions were conducted daily. In each probe trial, a food pellet was introduced into 1 well and the monkey retrieved the pellet.

The order of wells used was randomly assigned. Five trials were conducted in each of the 5 wells.

After the probe trials were completed, pellets were introduced into a testing well. Pellets were presented as rapidly as the monkey retrieved them. The training session ended after 30 min or after the monkey had not retrieved a pellet for 5 consecutive minutes. The testing well, or wells, was determined using the monkey's performance on the previous day. On the 1st day of training, the largest well was the testing well. If the monkey retrieved a high criterion (HC) number of pellets from the testing well, the next smallest well was used as the testing well the next day. The high criterion number of pellets was set to 600 pellets, which is the typical daily weight of food eaten by a monkey ad libidum. If the monkey did not retrieve the HC number of pellets, but retrieved more pellets than a low criterion (LC), the testing well did not change the next day. If the monkey retrieved a number of pellets lower than the LC, the next day, 75% of trials would be introduced into the same well used on the previous day, and 25% of trials would be introduced into the next largest well. The training series was complete when the monkey had retrieved the HC number of pellets out of the smallest well for 2 consecutive days. Monkeys took an average of 23.6 ± 8.9 days to reach criterion in prelesion training.

For most monkeys, the HC number of pellets was 600 and LC was 500. However, if the monkey weighed less than 700 g, the HC and LC were lowered to 500 and 400, respectively. Smaller animals were rarely able to eat 600 pellets per day, even when pellets were introduced into the largest well.

After the monkey reached HC on 2 consecutive days on the smallest well, random probe trials were conducted over the next 2 days. Each day, 2 sessions of 50 trials were conducted.

All probe trial and training sessions were videotaped using a video camera (Sony).

**Postlesion testing procedure—**After the mapping and cortical lesion procedures, monkeys were returned to their home cage. By postlesion days 3 to 6, most animals would again retrieve pellets from the Klüver board wells. On the 1st 2 days postinfarct that the animal would retrieve pellets, hand preference determination was conducted using the same method that had been used before the lesion, that is, without the restraint jacket (see above). Postlesion hand preference was one of several methods used to gauge the severity of the impairment caused by the lesion.

After the postlesion hand preference had been documented, monkeys were fitted with the restraint jacket that restrained the arm ipsilateral to the lesion. Thus, the monkeys were encouraged to use their more impaired hand to retrieve pellets during postlesion testing.

The postlesion testing procedure was identical to the prelesion training procedure (see above). Postlesion testing was completed when the monkey reached HC on 2 consecutive days on the smallest well. Monkeys took an average of 26.3 ± 6.3 days to reach criterion in postlesion testing. Random probe trials were then conducted over the next 2 days. Each day, 2 sessions of 50 trials were conducted.

## Neurophysiologic Methods

**Intracortical microstimulation methods—**After training was complete, animals were sedated with ketamine, 20 mg/kg i.m. Monkeys were intubated, and the femoral vein was catheterized. During the entire procedure, body temperature was maintained using a homeothermic blanket system (Harvard, Holliston, MA) and respiration rate, $CO_2$ output, heart rate, and blood saturated oxygen were continuously monitored.

Monkeys were placed into a stereotaxic frame and were given a mixture of nitrous oxide:oxygen (750:250 ml/h) and halothane (1.5%–3% as needed) anesthetic. Under sterile conditions, a 1.5 cm diameter portion of skull over the precentral gyrus containing the hand representation of M1 was removed. The exposed dura was removed, and a plastic chamber was secured to the skull surrounding the opening. The chamber was filled with sterilized silicone oil warmed to 38 °C.

After the surgical opening was complete, nitrous oxide/oxygen/halothane anesthesia was withdrawn and a combination of ketamine (20 mg/h) and acepromazine (0.01 mg/h) or valium (0.01 mg/h) anesthesia was used for the mapping procedure. A photograph of the exposed cortex was taken with a digital camera and imported into a graphics program (Canvas, Deneba Co, Saanichton, British Columbia). A 250 $mm^2$-interval grid was superimposed onto the photo of the cortex. At each grid crosspoint, a 3.5 M NaCl-filled glass electrode, with a tip diameter of 10 to 25 μm and an impedance of 400 to 1000 kΩ, was introduced perpendicular to the cortex to a depth of 1700 to 1800 μm using a micropositioner (Kopf, Tujunga, CA). A series of 40 ms current trains of thirteen 200 μs monophasic cathodal pulses (350 Hz) was then delivered at a rate of 1/s. If a grid cross-point marked an area over a blood vessel, the electrode was introduced immediately outside the vessel as close as possible to the grid intersection. At each site, the movement evoked at threshold and at 20 μA was defined. Movements of the digits, wrist, forearm, elbow, shoulder, and face were documented. Cortical microstimulation continued until a border of elbow, shoulder, and face representations or nonresponsive sites surrounded all movement representations of the digits and wrist. Prelesion maps contained approximately 300 to 350 sites. Figure 2 shows an example of a prelesion motor map superimposed on a photograph of the cortical surface.

After completion of the mapping procedure, ketamine/acepromazine or ketamine/valium anesthesia was withdrawn, and the halothane and nitrous oxide:oxygen anesthesia was given. An ischemic cortical lesion was made to approximately 45% of the M1 hand representation (see below).

After the lesion was made, the cranial opening was closed and the animal was recovered from anesthesia.

**Cortical lesion procedure—**An ischemic cortical lesion was targeted to 40% to 45% of the M1 hand representation. Each lesion was targeted to a region of the M1 hand area containing primarily digit representations. Due to the mosaic arrangement of digit and wrist representations within the M1,45,46 it was not possible to restrict the lesion to digit representations alone. However, lesions were targeted to the largest contiguous digit representation.

Surface blood vessels supplying the targeted area of the cortex were permanently occluded using microforceps connected to a bipolar coagulator. All blood vessels within the targeted area were also permanently occluded. After the lesion was made, the exposed cortex was observed for 30 to 60 min to watch for reperfusion of any blood vessels that had been occluded. If any reperfusion was observed, the blood vessel was recauterized. Figure 3 shows a photograph of exposed cortex before and immediately after an ischemic lesion.

**Mapping procedure after postrehabilitative testing—**Following the postlesion testing procedure and concomitant behavioral recovery, a 2nd intracortical microstimulation (ICMS) mapping procedure was conducted using procedures identical to those described above for the prelesion mapping procedure.

**Histological procedure—**After the postrehabilitative testing mapping procedure was complete, animals were deeply anesthetized with a lethal dose of pentobarbital and perfused with 0.9% phosphate-buffered saline followed by 4% phosphate-buffered paraformaldehyde fixative. The brain was removed and cut into 50 μm parasagittal sections. The area 3a/4 border was defined cytoarchitectonically, and the extent of the lesion was verified. A photograph of a histologically processed lesion can be found in Figure 2F of a previous study.14

The histological procedure was useful in verifying that the lesion extended through all layers of cortex, but the histological procedure cannot be used to accurately define the extent of the lesion. After several weeks survival after the lesion, substantial necrosis and scavenging of the tissue within the lesion occurs. Therefore, less direct methods were used to estimate lesion size.47 Prelesion and postlesion digital photographs were used to estimate lesion volume.40 Immediately after the lesion was made, the damaged cortex became blanched in color. Thus, the lesion could be easily seen in postlesion photographs. Postlesion photographs of intact vasculature were superimposed onto prelesion photographs, enabling the determination of the cortical territory spared by the lesion. Example pre- and postlesion photographs are shown in Figure 2 of a previous article.40 Using these methods, the areal extent of the cortical surface destroyed by the lesion (in $mm^2$) was estimated. Lesion size for each case, in absolute measures ($mm^2$) and percent of hand representation, is summarized in Table 1.

### Data Analysis

**Assessment of changes in cortical maps—**Cortical mapping results were recorded on a grid superimposed on a photograph of the cortical surface. A custom, in-house computer algorithm was used to construct a 2-dimensional map of movement representations using the coordinates of electrode penetrations. A graphics program (NIH Image, developed at the US National Institutes of Health and available on the Internet at http://rsb.info.nih.gov/nih-image/) was used to determine the size of digit and wrist/forearm movement representations (in $mm^2$).

To make comparisons between prelesion and postlesion maps, the lesion was masked in both maps. Thus, only changes in the maps outside of the lesion area were determined. Percent change in area after the lesion was calculated by dividing the postlesion areal measurement by the prelesion areal measurement for each movement category.

### Statistical Analyses

Descriptive statistics were performed on measurements of cortical areal changes. An arcsine transformation was used to normalize these data for parametric statistical analysis. One-way analysis of variance and Fisher's protected least significant difference (PLSD) analyses were used to compare changes in cortical topography between different groups of animals.

## RESULTS

This study compared cortical maps of the M1 hand representation before and approximately 1 month after a lesion to the rostral portion of the M1 hand representation (M1r). Changes in cortical topography after M1r lesions were then compared to previously published results describing changes in cortical topography after M1c lesions.

### Changes in Cortical Topography After Rostral M1 Lesions

The sizes of the M1 prelesion and postrehabilitation maps (in $mm^2$) were calculated (see Methods). The lesion area was masked from the analysis of both prelesion and postrehabilitation maps. Thus, analyses were conducted on the representational area that had

been spared by the lesion. Figure 4 shows prelesion and postrehabilitation maps from all animals, as well as percent changes in spared representational area for each animal.

After rehabilitative training, 3 of the 4 animals displayed a small increase in total spared hand representation (i.e., the size of the hand representation surrounding the lesion). Hand area decreased substantially in the 4th animal, likely due to differences in behavioral experience (see below). On average, the size of the spared hand representation decreased 1.2%, compared to the prelesion map size (*SD* = 18.3; range −28.1% to +11.52%) (Fig. 4).

The hand representation size measurements were separated for further analyses into digit and wrist/forearm areal measurements. The average amount of digit area decreased from prelesion levels 4.7% (*SD* = 22.4; range −21.3% to +28.4%). The amount of wrist/forearm area decreased an average of 0.5% (*SD* = 26.7; range −33.3% to +27.9%). Changes in area size for each animal are shown in Figure 4, whereas group averages are shown in Figure 5.

In 1 animal, the mapping results were markedly different from the 3 others. In this animal (0112), the spared hand representation decreased by 28%. Differences in behavioral experience may explain the differences in the mapping results. This animal did not complete the rehabilitative training protocol in the same manner as the other animals. After the lesion, the animal showed an initial motor deficit that quickly resolved over the period of postlesion training. However, the monkey never reached criterion on wells 2 through 5 during training, although the animal did display an improvement in motor skill on the daily probe trials. Thus, the monkey was trained during the month after the lesion entirely on wells 1 and 2 (the largest wells), although motor skill was tested each day on all wells in the probe trials. One month after the lesion, the motor performance index of case 0112 was not different from the other animals in the rostral lesion group. To control for the timing of the postlesion map after the lesion between animals, the postlesion map was derived 1 month after the lesion. Additionally, this monkey had the largest lesion ($mm^2$ of M1 area destroyed) of the animals in this study.

## Correlations Between Map Changes and Behavioral Improvement

Relationships between map changes and improvements in motor skill were examined. Motor skill was assessed on the pellet-retrieval task. Behavioral changes after lesions and rehabilitative training are described in a previous article.37 Methods for behavioral analysis can be found in this previous study. Prelesion motor performance was not different between animals. Correlations were not found between percent improvement in motor performance and changes in wrist/forearm ($Z = -0.16$, $P > 0.98$) or total hand area ($Z = 0.31$, $P > 0.75$). One monkey (9502) had a substantially larger increase in digit area (28.3%) compared with the other monkeys (range −21.3% to −12.9%). Monkey 9502 also showed the largest improvement in motor skill after rehabilitation (258% improvement; other monkeys ranged from 110% to 153% improvement). However, due to the small sample size, and because the increase in digit area in monkey 9502 is an outlier, statistical assessment of correlations could not be done.

## Comparison of Map Changes After Rostral Versus Caudal M1 Lesions

The changes observed in cortical topography after M1r lesions were compared to changes previously reported in cortical topography after M1c lesions.14,15 These previous experiments have shown that after a lesion to the M1c hand representation, if monkeys did not receive any rehabilitative intervention, the size of the spared M1 hand representation decreased 52%.14 Alternatively, if monkeys received daily rehabilitative training of the impaired hand, using the same training protocol that was used in the present experiment (see Methods), the size of the spared M1 hand representation increased 9%.14 The sizes of the caudal lesions were not statistically different from the sizes of the rostral lesions used in the present study ($P > 0.12$).

Figure 5 depicts the percent change in spared cortical representational area 1 month after an M1r or M1c lesion.

An analysis of variance was performed on postlesion cortical changes in 3 groups of animals: caudal lesion +spontaneous recovery ("caudal spontaneous"),14 caudal lesion +rehabilitative training ("caudal training"),15 and rostral lesion +rehabilitative training ("rostral training"). There was a statistical effect of group on the percent change in total spared hand area 1 month after the lesion ($F = 11.54$, $P = 0.006$). Fisher's PLSD post hoc analyses revealed a statistically significant difference between the caudal spontaneous and caudal training groups ($P = 0.002$). A statistically significant difference also existed between the caudal spontaneous and rostral training groups ($P = 0.007$). There was no statistical difference between the caudal training and rostral training groups ($P = 0.255$).

There was also a statistical effect of group on the percent change in digit representational area 1 month after the lesion ($F = 8.40$, $P = 0.014$). Fisher's post hoc analyses revealed a statistically significant difference between the caudal spontaneous and caudal training groups ($P = 0.007$). A statistically significant difference also existed between the caudal spontaneous and rostral training groups ($P = 0.008$). There was no statistical difference between the caudal training and rostral training groups ($P = 0.899$).

There was no statistical effect of group on the percent change in wrist/forearm representational area 1 month after the lesion ($F = 2.14$, $P = 0.189$).

## DISCUSSION

The present study documents changes in motor cortex physiology following a lesion to the rostral portion of the M1 hand representation and postlesion rehabilitative training of the hand contralateral to the lesion. These changes were then compared to previously published changes in motor cortex physiology following a lesion to the caudal portion of the M1 hand representation in the absence or presence of postlesion rehabilitative training of the hand contralateral to the lesion. Inasmuch as lesions to the squirrel monkey M1r versus M1c produce different behavioral deficits,37 the present study was conducted to compare changes in cortical physiology after M1r versus M1c lesions.

### Changes in Intracortical Microstimulation Maps of the M1 Hand Area After Rostral M1 Lesions

The present experiments compare the size of the M1 hand representation before an M1r lesion to the size of the hand representation after 1 month of postlesion rehabilitative training on a pellet-retrieval task. After M1r lesions and rehabilitative training, monkeys retained spared hand area, similar in result to M1c lesions and rehabilitative training.15

It is evident that the percent change in the spared hand area after rehabilitation was substantially lower in 1 case (0112) than in the other 3 cases. Two reasons may account for this deviation from the results of the other animals. First, this animal did not complete the rehabilitative training protocol in the same manner as the other animals. It is possible that the cortical changes observed after rehabilitative training are dependent upon repetitive training on the smaller wells that maximize retraining of skilled manual performance. Second, this monkey had the largest lesion ($mm^2$ of M1 area destroyed) of the animals in this study, although the relative lesion size was not the largest.

## Comparison of Changes in Intracortical Microstimulation Maps of the M1 Hand Area After Rostral Versus Caudal M1 Lesions

The cortical changes seen after M1r lesions were compared to previously published cortical changes observed after M1c lesions14,15 (Fig. 5). There was no statistical difference in the percent change in spared representational area after rehabilitative training following an M1r versus an M1c lesion. However, map changes in both of these groups were different from those observed after an M1c lesion and spontaneous recovery (i.e., no rehabilitative training). After caudal M1 lesions, without rehabilitation, the hand area surrounding the lesion is reduced in size, primarily due to loss of digit territories. Regardless of whether the lesion is in M1c or M1r, rehabilitative training appears to prevent this loss of hand/digit area (except in 1 of the 4 M1r cases in the present study). However, there was considerable variability in the wrist/forearm representations following M1c lesions, and thus, no conclusions regarding this region can yet be made.

This result suggests that maximal retention of representational area outside of the lesion may require behavioral retraining of *skilled use* of the impaired hand after the lesion, regardless of the specific location of the lesion within the M1 hand representation. A further study is required to assess changes in cortical topography after an M1r lesion in the absence of postlesion rehabilitative training.

## Correlations Between Map Changes and Behavioral Improvement

There were no correlations between percent improvement in motor performance and changes in total hand or wrist areal changes. The monkey with the greatest improvement in motor skill also had the largest increase in digit area after rehabilitation. Although clear conclusions cannot be drawn here owing to the percent digit area change in 9502 being considered an outlier, the result suggests that there may be a behavioral correlate of the increased digit area after rehabilitation. A previous mapping study in monkeys with caudal M1 lesions showed a correlation between behavioral improvement and an increase in motor cortical area producing coactivation of digit and elbow/shoulder joints after rehabilitation.48 This supports the hypothesis that cortical changes correlate with behavioral improvements.

## Cortical Reorganization Following Brain Injury

Cortical reorganization after brain injury may play an adaptive role in recovery of function. Cortical reorganization has been observed after lesions in sensory and motor cortical areas. For example, after lesions to somatosensory cortex area 3b in monkeys and postlesion training on a pellet-retrieval task, sensory responses emerged in areas 3a and 3b that corresponded with the skin surfaces used in the pellet-retrieval task.49 After motor cortex lesions, the representational areas surrounding the lesion can decrease in size if the animals did not receive rehabilitative training.14 Alternatively, if animals receive rehabilitative training, the representational area that was contained within the lesion may emerge in the tissue surrounding the lesion.15–7,49 Additionally, when human stroke patients were encouraged to use the impaired arm to complete motor tasks, the size of the arm muscle representations, as measured by transcranial magnetic stimulation, increased in the affected hemisphere.50

In a previously published study, the role of skilled use in the retention of spared cortical territory following an M1c lesion was explored in greater detail.40 A group of animals received a lesion to the caudal portion of the M1 hand representation and was fitted with a jacket that restrained their unimpaired hands, encouraging the animals to use the impaired hand in normal cage activities. However, these animals did not receive rehabilitative training on the pellet-retrieval task. After 1 month, the spared hand representation in these animals was reduced to the same size as animals that had not received any type of postlesion intervention. That study suggested that mere use of the impaired hand is not sufficient to drive adaptive cortical changes; skilled

use of the impaired hand is required. The present study further supports this finding, in that animals retained the prelesion levels of spared hand area after receiving postlesion rehabilitative training.

Studies of neurophysiological correlates of normal motor behavior demonstrate that cortical changes are dependent upon motor skill learning, not simply motor use. When monkeys were trained on motor tasks requiring skilled use of the hand, the hand representation in M1 expanded.13 Alternatively, when monkeys were trained to retrieve food pellets from a large well, which did not require skill learning, motor maps did not change.51 Likewise, in rats, motor maps change in response to skill learning but not in response to motor use in the absence of skill learning.12,52 Thus, both learning- and injury-induced plasticity in the motor cortex seem to be driven by skill learning and not motor use alone.

One unexpected result in the present study provides further evidence that adaptive cortical plasticity after a lesion is dependent upon repetitive skill training, not only motor use. Case 0112 was trained after the lesion on only the larger wells of the Klüver board because the monkey did not meet criteria to advance to the smaller wells during training. As shown in Figure 4, this animal lost more of the hand representation surrounding the lesion than any other animal in the study. This outcome is consistent with the spontaneous recovery and jacket-restrained groups such that skill learning, and not just simple motor use, may be needed to drive adaptive motor cortical changes.

### Implications for Stroke Rehabilitation

The results of the present study augment several studies of human stroke recovery in which stroke patients are encouraged to use the arm contralateral to the stroke during activities of daily living and during sessions of intensive physical therapy. This therapeutic technique has been termed constraint-induced movement therapy, or CI therapy, and has been studied in detail by Taub, Wolf, and colleagues.41–44,53,54 During CI therapy, chronic stroke patients wear a sling or mitt to restrict the arm ipsilateral to their stroke. This constraint device encourages patients to use their more impaired arm, the arm contralateral to the stroke. In early CI therapy studies, after chronic stroke patients had worn the constraint device for 2 weeks, there was an improvement in motor activity of the patient that was sustained for at least 2 years after the CI therapy treatment.41 Another group of patients wore the constraint device over their unaffected arm and also received intensive daily training of the affected arm for up to 6 h per day. These patients showed even more improvements in motor ability after the 2-week treatment than patients not receiving intensive therapy using the impaired arm.54 Changes in cortical physiology matched improvements in motor activity. Motor cortical representations of the muscles of the affected arm increased in size after 2 weeks of CI therapy treatment.50, 55

The present study complements the results of CI therapy treatments. In both sets of experiments, adaptive cortical changes were maximally achieved by intensive training of the impaired hand after the cortical injury. These results provide encouraging support for the use of postlesion rehabilitative treatments that engage the impaired arm in skilled movements.

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**Figure 1.**
Squirrel monkey at Klüver board. The monkey is wearing a jacket with a mesh sleeve over the nondominant arm. This jacket encouraged the animal to retrieve pellets using its dominant hand.

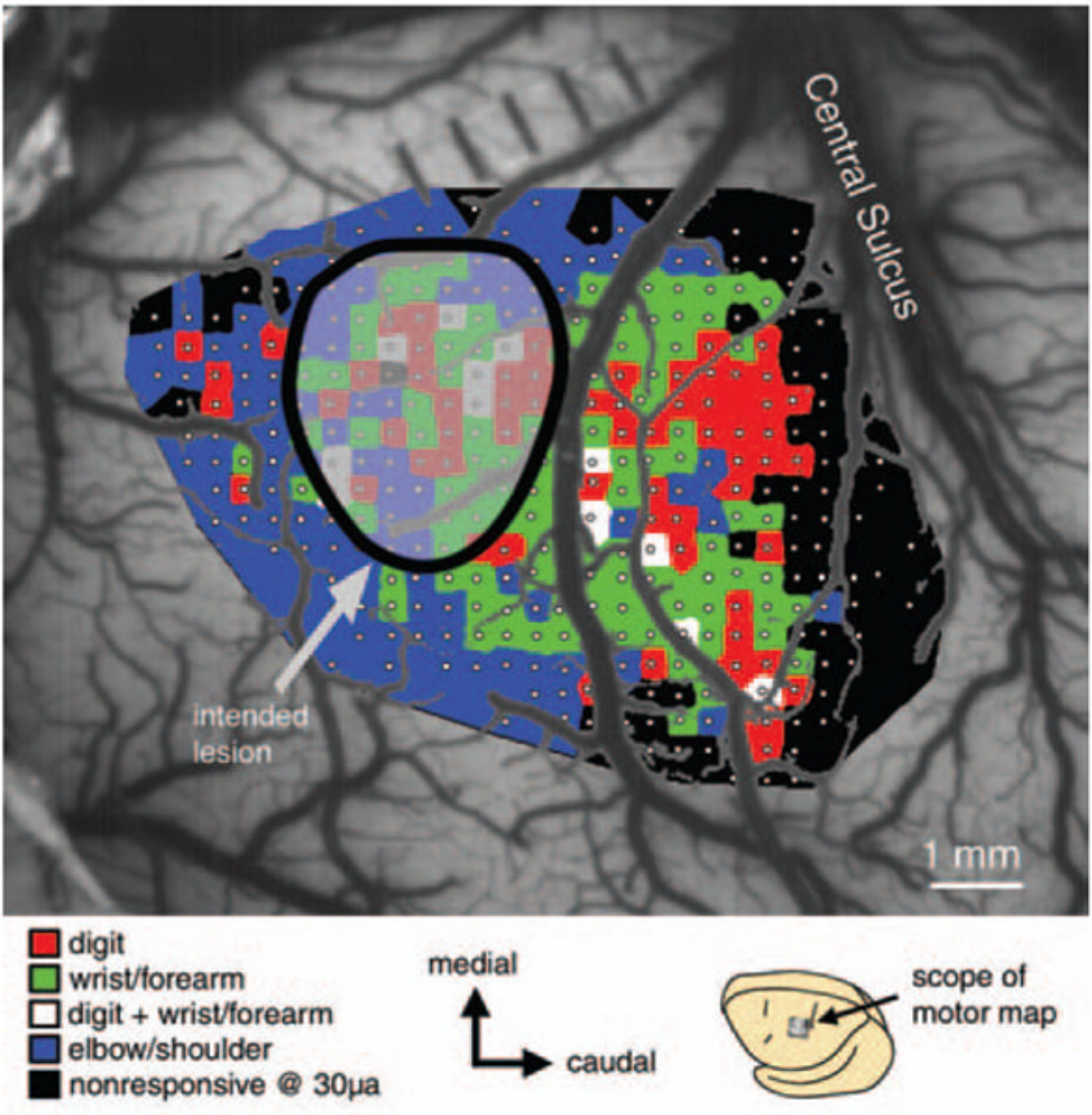


**Figure 2.**
Prelesion intracortical microstimulation–derived motor map of the primary motor cortex distal forelimb representation superimposed onto a photograph of the cortical surface (monkey 0112; rostral lesion group). Small white circles denote electrode penetration points. A computer algorithm was used to construct a color-coded graphic representation of movements evoked at penetration sites.

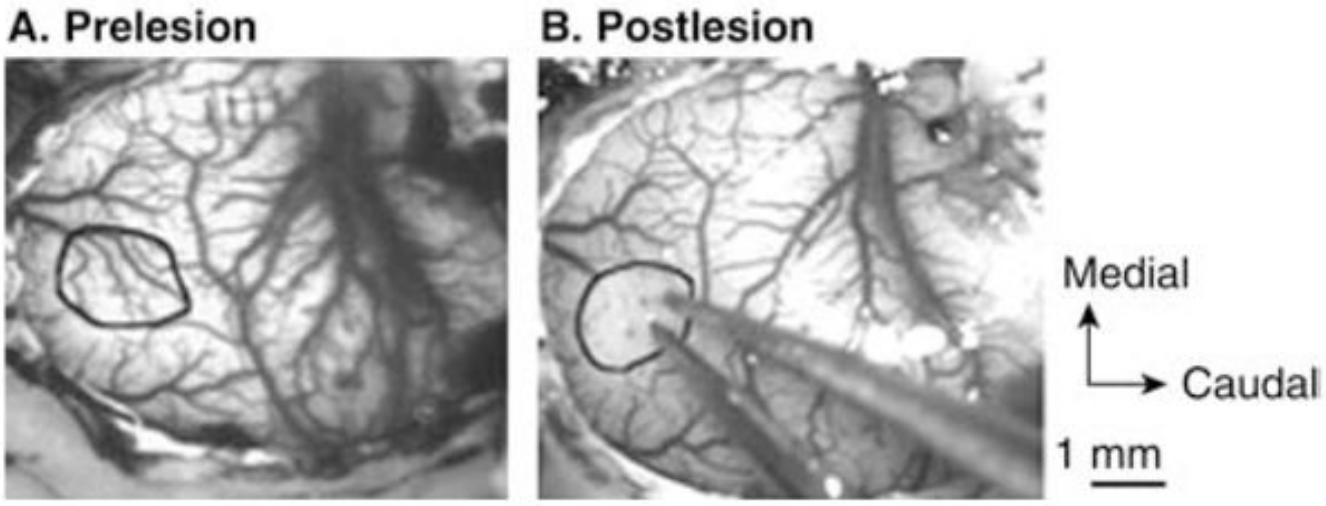


**Figure 3.**
Photographs of cortical surface (A) immediately before and (B) immediately after electrocoagulation of surface vessels within the intended lesion location. Microforceps, seen in panel B, are connected to a bipolar coagulator and are used to cauterize the targeted vessels.

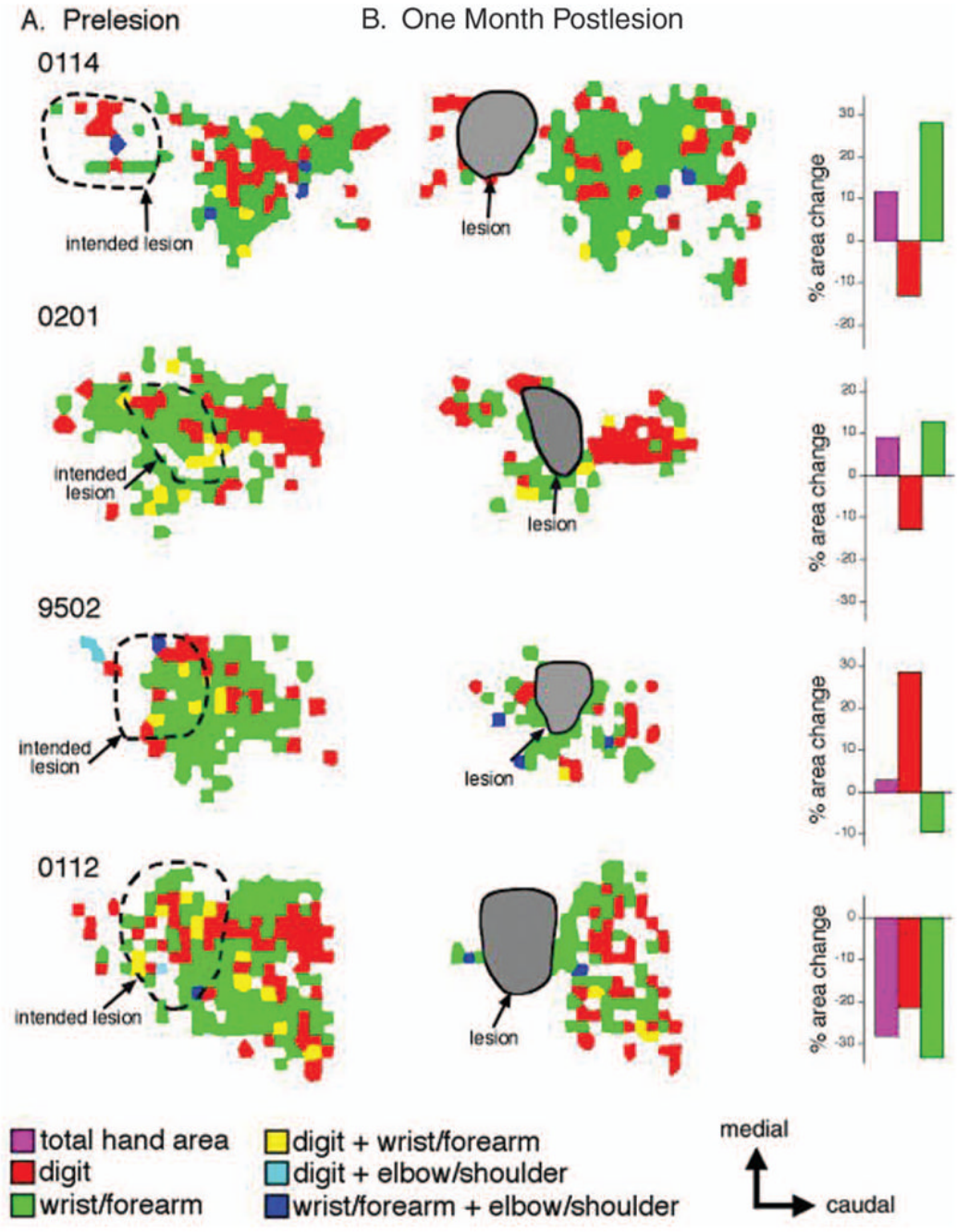


**Figure 4.**

Prelesion (A) and 1 month postlesion (B) maps of the primary motor cortex distal forelimb representation in all animals. Maps are color coded to denote movement representations for different portions of the distal forelimb. Graphs show the percent change in spared hand area 1 month postlesion for 3 movement categories: total hand area (magenta), digit area (red), and wrist/forearm area (green).

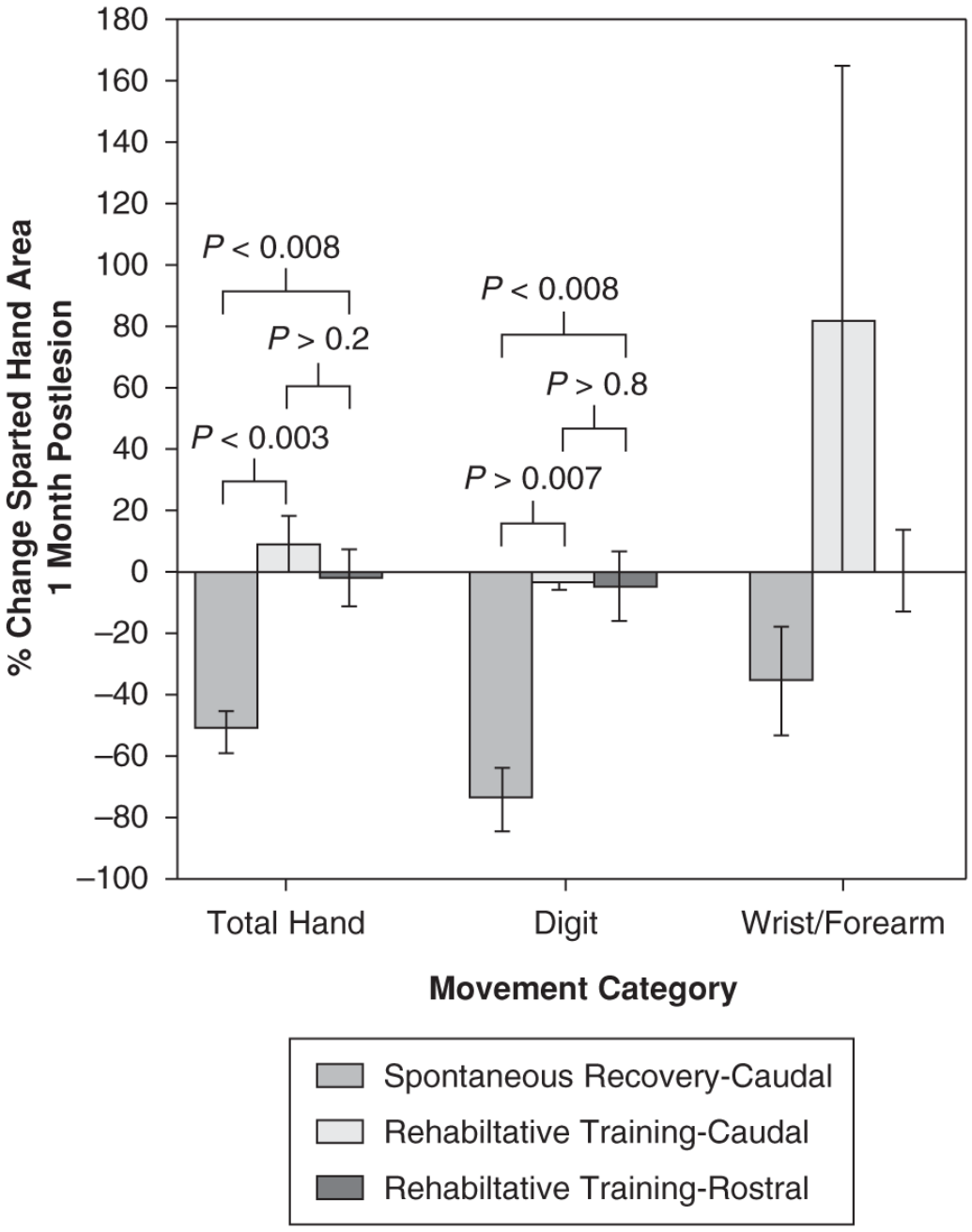


**Figure 5.**

Percent change in spared representational area 1 month after a caudal or rostral primary motor cortex lesion. Three groups of animals were compared: caudal lesion +spontaneous recovery ($n = 2$), caudal lesion +rehabilitative training ($n = 4$), and rostral lesion +rehabilitative training ($n = 4$). Both the caudal lesion +rehabilitative training and the rostral lesion +rehabilitative training groups retained significantly more total hand area and more digit area than the caudal lesion +spontaneous recovery ($P < 0.01$). There were no statistically reliable differences between the caudal and rostral lesion +rehabilitative training groups.

**Table 1**

Size of Hand Representation, Size of Lesion, and Percentage of Hand Representation Destroyed by the Lesion for Each Monkey

| Case | Size of Hand Representation ($mm^2$) | Lesion Size($mm^2$) | Relative Size of Lesion (% Hand Representation) |
|---|---|---|---|
| 0112 | 12.39 | 5.42 | 43.74 |
| 0114 | 9.40 | 4.44 | 47.23 |
| 0201 | 10.57 | 2.82 | 26.68 |
| 9502 | 6.00 | 3.87 | 64.50 |